

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



D16

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> :

C07H 21/04, C07K 1/00, 16/00, C12N  
15/00, 1/20, C12P 21/06, A61K 38/00,  
C12Q 1/68, G01N 33/53, 33/566

A1

(11) International Publication Number:

WO 99/47540

(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/US99/05804

(22) International Filing Date: 18 March 1999 (18.03.99)

(30) Priority Data:

60/078,566	19 March 1998 (19.03.98)	US
60/078,576	19 March 1998 (19.03.98)	US
60/078,573	19 March 1998 (19.03.98)	US
60/078,574	19 March 1998 (19.03.98)	US
60/078,579	19 March 1998 (19.03.98)	US
60/078,578	19 March 1998 (19.03.98)	US
60/078,581	19 March 1998 (19.03.98)	US
60/078,577	19 March 1998 (19.03.98)	US
60/078,563	19 March 1998 (19.03.98)	US
60/080,314	1 April 1998 (01.04.98)	US
60/080,312	1 April 1998 (01.04.98)	US
60/080,313	1 April 1998 (01.04.98)	US

(71) Applicant (for all designated States except US): HUMAN  
GENOME SCIENCES, INC. [US/US]; 9410 Key West  
Avenue, Rockville, MD 20850 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): RUBEN, Steven, M.  
[US/US]; 18528 Heritage Hills Drive, Olney, MD 20832

(US). NI, Jian [CN/US]; 5502 Manorfield Road, Rockville,  
MD 20853 (US). ROSEN, Craig, A. [US/US]; 22400  
Rolling Hill Road, Laytonsville, MD 20882 (US). YU,  
Guo-Liang [CN/US]; 242 Gravett Drive, Berkeley, CA  
94705 (US). YOUNG, Paul, E. [US/US]; 122 Beckwith  
Street, Gaithersburg, MD 20878 (US). FENG, Ping  
[CN/US]; 4 Relda Court, Gaithersburg, MD 20878 (US).  
SOPPET, Daniel, R. [US/US]; 15050 Stillfield Place,  
Centreville, MD 22020 (US). WEI, Ying-Fei [CN/US];  
242 Gravett Drive, Berkeley, CA 94705 (US). ENDRESS,  
Gregory, A. [US/US]; 9729 Clagett Farm Drive, Potomac,  
MD 20854 (US). DUAN, Roxanne, D. [US/US]; 5515  
Northfield Road, Bethesda, MD 20817 (US). KYAW, Hla  
[MM/US]; 520 Sugarbush Circle, Frederick, MD 21703  
(US). EBNER, Reinhard [DE/US]; 9906 Shelburne Terrace  
#316, Gaithersburg, MD 20878 (US). LAFLEUR, David,  
W. [US/US]; 3142 Quesada Street, N.W., Washington, DC  
20015 (US). OLSEN, Henrik, S. [DK/US]; 182 Kendrick  
Place #24, Gaithersburg, MD 20878 (US). SHI, Yanggu  
[CN/US]; 437 West Side Drive #102, Gaithersburg,  
MD 20878 (US). MOORE, Paul, A. [US/US]; 19005  
Leatherbark Drive, Germantown, MD 20874 (US).

(74) Agents: BROOKES, A., Anders et al.; Human Genome  
Sciences, Inc., 9410 Key West Avenue, Rockville, MD  
20850 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR,  
BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE,  
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,  
MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,  
SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW,  
ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG,  
ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ,  
TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI,  
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE,  
SN, TD, TG).

Published

With international search report.

(54) Title: 95 HUMAN SECRETED PROTEINS

(57) Abstract

The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## 95 Human Secreted Proteins

### *Field of the Invention*

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and their production.

### *Background of the Invention*

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include the commercially valuable human insulin, interferon, Factor VIII, human

growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent  
5 medical disorders by using secreted proteins or the genes that encode them.

### ***Summary of the Invention***

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells,  
10 antibodies, and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

15

### ***Detailed Description***

#### **Definitions**

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

20 In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of  
25 matter, or particular cell is not the original environment of the polynucleotide.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released  
30 into the extracellular space, the secreted protein can undergo extracellular processing



to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are less than 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, or 7.5 kb in length. In a further embodiment, polynucleotides of the invention comprise at least 15 contiguous nucleotides of the coding sequence, but do not comprise all or a portion of any intron. In another embodiment, the nucleic acid comprising the coding sequence does not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene in the genome).

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an

overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

- 5           Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or
- 10   temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl: 0.2M NaH<sub>2</sub>PO<sub>4</sub>; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent
- 15   hybridization can be done at higher salt concentrations (e.g. 5X SSC).

- Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and
- 20   commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

- Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a
- 25   complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

- The polynucleotide of the present invention can be composed of any
- 30   polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of

single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation,

gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

5 (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

10 "SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the  
15 present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not  
20 more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

### **Polynucleotides and Polypeptides of the Invention**

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 1**

This gene is expressed primarily in anergic T cells and merkel cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
30 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders and inflammatory diseases. Similarly, polypeptides

and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 108 as residues: Ala-55 to Gln-64.

The tissue distribution in T-cells and merkel cells indicates that the protein products of this gene are useful for the diagnosis and/or treatment of immune system diseases. Furthermore,

15 Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by  
20 boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune  
25 deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a  
30 tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2329 of SEQ ID NO:11, b is an integer of 15 to 2343, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 2

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: IPENRRPASXCTWSMWTSRTTTRPPWGRFSSVSSASV SSTRKTRWRTRSTSCCRSSRRRVAAPFCTPSASTEPSARMEPPLELPVVHTFSFLT  
TFVFTYRCSAGDGSITQINCA YEMGEEMPKRQMKAIKFLLFHFYL (SEQ ID NO:205), IPENRRPASXCTWSMWTSRTTTRPPWGRFSSVSSASVSST (SEQ ID NO:206), RKTWRTRSTSCCRSSRRRVAAPFCTPSASTEPSARMEPPLELP (SEQ ID NO:207), and/or VVHTFSFLTTFVFTYRCSAGDGSITQINCA YEMGEEMPKRQ  
MKAIKFLLFHFYL (SEQ ID NO:208). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in placental, brain and breast tissues, and to a lesser extent in T cells and tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative and/or endocrine disorders and neoplasias, or developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurodegenerative, developing, endocrine and

immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, endocrine, immune, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken  
5 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 109 as residues: Ala-55 to Asn-60, Lys-65 to Met-71, Leu-75 to Asn-86, Asp-93 to  
10 Asp-110, Leu-130 to Cys-138, Gln-149 to Glu-154, Thr-172 to Ile-179, Glu-185 to Arg-192.

The tissue distribution in breast and brain tissues indicates that the protein products of this gene are useful for the diagnosis and/or treatment of endocrine disorders, neurodegenerative disorders, developmental disorders, immune system  
15 diseases and neoplasias. The tissue distribution in placental tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be  
20 produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus.

Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in  
25 vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Likewise,

Expression of this gene product in T-cells indicates a role in the regulation of  
30 the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be

involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1163 of SEQ ID NO:12, b is an



integer of 15 to 1177, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 3

5 The translation product of this gene shares sequence homology with bovine beta-mannosidase, which is thought to be important in lysosomal catabolism of glycoproteins. See, for example, J. Biol. Chem. 270, 3841-3848 (1995), incorporated herein by reference in its entirety. Based on the sequence similarity between these proteins the translation product of this gene will sometimes hereinafter be referred to  
10 as human beta-mannosidase. Human beta-mannosidase is expected to share certain biological activities, particularly enzymatic activities, with bovine beta-mannosidase. Such activities may be assayed by methods known in the art, described in J. Biol. Chem. 270, 3841-3848 (1995), and/or disclosed elsewhere herein.

In specific embodiments, polypeptides of the invention comprise the following  
15 amino acid sequences: HPSIIWSGNNENEEALMMNWHISFTDRPIYIKDYVTL YVKNIRELVLAGDKSRPFITSSPTNGAETVAEAWVSQNPNSNYFGDVHFDYDI SDCWNWKVFPKARFASEYGYQSWPSFSTLEKVSSTEDWSFNSKFSLRQHHEGGNKQMLYQAGLHFKLPQSTDPLRTFKDTIYLTQVMQAQCVKTETEFYRRS RSEIVDQQGHTMGALYWQLNDIWQAPSW (SEQ ID NO:209), and/or  
20 VRVHTWS SLEPVCSRVTFRFVMKGGAEVCLYEPPVSELLRRCGNCTRESCVVSFYLSAD HELLSPTNYHFLSSPKEAVGLCKAQITAIISQQGDIFVFDLETSAPFVWLDV GSIPGRFSDNGFLMTEKTRTILFYWPWEPTSKNELEQSFHVTSLTDIY (SEQ ID NO:210). Polynucleotides encoding these polypeptides are also encompassed by the  
25 invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 4. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 4.

This gene is expressed primarily in colon tissue, and to a lesser extent in thymus stromal cells and chondrosarcoma tissue.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chondroma and mannosidosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the chondro and immune system. The expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, metabolic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to bovine beta-mannosidase indicates that the protein products of this gene are useful for the diagnosis and/or treatment of chondroma and mannosidosis. Human beta-mannosidosis is an autosomal recessive, lysosomal storage disease caused by a deficiency of the enzyme beta-mannosidase. Furthermore, the homology of the translation product of this gene to beta-mannosidase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as lysosomal storage deficiencies, Tay-Sachs disease, phenylketonuria, galactosemia, hyperlipidemias, porphyrias, and Hurler's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2093 of SEQ ID NO:13, b is an

integer of 15 to 2107, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 4

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: PRLTPRMKWPTAALASRLLGWTVLRPPYPRVPSLPQVT LHPTDGLMAVLYTGGEGR TLGEQHFFHETFVTRWLLGPVPVRFGACSP LSFL APRRGQGAPAGXFCACPRPASRQLCPWPALPGTPYSNSAPLCTGMGHSNTPQ GPPSPQYALSPTEPTSLSGNSHLPAILVL (SEQ ID NO:211),  
 10 PRLTPRMKWPTAAL ASRLLGWTVLRPPYPRVPSLPQVTLHP (SEQ ID NO:212), TDGLMAVLYTGGE GRTLGEQHFFHETFVTRWLLGPVPVRFG (SEQ ID NO:213), ACSPLSFLAPRRGQGAPAGXFCACPRPAS RQLCPWPALPGTP (SEQ ID NO:214), and/or  
 15 YSNSAPLCTGMGHSNTPQGPPSPQYALSPTEPTSLSGNS HLPAILVL (SEQ ID NO:215). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in human lung (adult and fetal), and to a lesser extent in liver and brain tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as  
 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, pulmonary disorders and hemostasis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of  
 25 disorders of the above tissues or cells, particularly of the lung and liver tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a  
 30 disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 111 as residues: Arg-28 to Gln-36.

The tissue distribution in lung and liver tissues indicates that the protein products of this gene are useful for the diagnosis and/or treatment of pulmonary disorders and hematopoietic disorders. The tissue distribution in adult and fetal lung tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Alternatively,

Expression of this gene product in liver tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general  
5 formula of a-b, where a is any integer between 1 to 1248 of SEQ ID NO:14, b is an integer of 15 to 1262, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 5

10 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: HLLVTPCRLPVPEFPGRTPRGSRTPD (SEQ ID NO:216). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in rapidly dividing liver tissue, (e.g., hepatoma, hepatocellular carcinoma, and fetal liver tissue), and to a lesser extent in  
15 normal liver tissue, and other tumors such as colon cancer and uterine cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, particularly hepatomas, colon cancer, and uterine cancer.

20 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, colon and uterus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, colon, uterus,  
25 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 112 as residues: Trp-35 to Trp-45, Pro-52 to Asp-57, Thr-73 to Arg-82, Pro-105 to Leu-112, Pro-115 to Arg-127, Pro-140 to Gln-151.

5 The tissue distribution in liver tissues and cancers thereof, as well as other cancerous tissues, indicates that the protein products of this gene are useful for the diagnosis and/or treatment of cancers, particularly, hepatoma, colon cancer and uterine cancer, as well as cancers of other tissues where expression has been observed. Furthermore, expression within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 745 of SEQ ID NO:15, b is an integer of 15 to 759, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 6**

This gene is expressed primarily in hepatocellular tumors.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatomas. Similarly, polypeptides and antibodies directed to these

30

polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 113 as residues: Pro-32 to Gly-40.

The tissue distribution in hepatocellular tumors indicates that the protein products of this gene are useful for the diagnosis and/or treatment of hepatomas, as well as cancers of other tissues where expression has been observed. Furthermore, expression within cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1796 of SEQ ID NO:16, b is an integer of 15 to 1810, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 7**

This gene is expressed primarily in human rhabdomyosarcoma tissue, as well as in placental tissue.

5           Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, malignant neoplasms and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing  
10 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
15 synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:  
20 114 as residues: Arg-23 to Trp-28, Phe-93 to Lys-98, Arg-199 to Trp-206, Gly-208 to Met-213.

The tissue distribution in placental tissue and human rhabdomyosarcoma tissue indicates that the protein products of this gene are useful for the diagnosis and/or treatment of skeletal and reproductive disorders. Furthermore, the tissue  
25 distribution in placental tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then  
30 transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus.



Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1038 of SEQ ID NO:17, b is an integer of 15 to 1052, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 8

This gene is expressed primarily in fetal liver/spleen and fetal skin tissues, and to a lesser extent in breast cancer tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders and neoplasias. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal tissue and adult immune system, expression of this gene at significantly higher or lower levels may be

5 routinely detected in certain tissues or cell types (e.g., developing, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

10 The tissue distribution in fetal liver/spleen and skin tissues indicates that the protein products of this gene are useful for the diagnosis and/or treatment of developmental disorders and malignant neoplasias. Likewise, expression within fetal tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, fetal development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy.

15 Alternatively, the tissue distribution in fetal skin tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. Moreover, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

20

25

30

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1116 of SEQ ID NO:18, b is an integer of 15 to 1130, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 9

The translation product of this gene shares sequence homology with the bacterial gufA gene, as well as a *C. elegans* protein of unknown function.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: MIPGSDSQTALNFGSTLMKKKSDPEGPALLFPESELSIRI GRAGLLSDKSENGEAYQRKKAAATGLPEGPAVPVPSRGNLAQPGGSSWRRI ALLILAITIHNVPGLAVGVGFGAIEKTASATFESARNLAIGIGIQNFPEGLAVS LPLRGAGFSTWRAFWYGQLSGMVEPLAGVFGAFVLAEPILPYALAF AAG AMVYVVMDDIPEAQISGNGKLASWASILGFVVMMSLDVGLG (SEQ ID NO:217), MIPGSDSQTALNFGSTLMKKKSDPEGPALLFPESELSIRIGRA (SEQ ID NO:218), GLLSDKSENGEAYQRKKAAATGLPEGPAVPVPSRGNLAQPG ( S E Q I D N O : 2 1 9 ) , GSSWRRIALLILAITIHNVPGLAVGVGFGAIEKTASATFESAR (SEQ ID NO:220), NLAIGIGIQNFPEGLAVSLPLRGAGFSTWRAFWYGQLS GMVEP (SEQ ID NO:221), LAGVFGAFVLAEPILPYALAF AAGAMVYVVMDDIPEAQIS (SEQ ID NO:222), and/or GNGKLASWASILGFVVMMSLDVGLG (SEQ ID NO:223). Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in cells of the immune system, particularly macrophage.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the immune system, such as AIDS, as well as

5 inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell  
10 types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

15 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in immune cells such as macrophage indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages,  
20 including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
25 and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of  
30 various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in macrophage also strongly indicates a role

for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or  
10 more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 869 of SEQ ID NO:19, b is an integer of 15 to 883, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 10**

This gene is expressed primarily in the spleen metastatic melanoma tissue as well as in embryonic tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a  
20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the spleen or immune system, developmental disorders, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above  
25 tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., spleen, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene  
30 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO: 117 as residues: Asn-37 to Lys-44, Ser-73 to Glu-78, Ala-103 to Ser-111.

The tissue distribution in spleen metastatic melanoma and embryonic tissues indicates that the protein products of this gene are useful for the diagnosis and/or treatment of disorders affecting the spleen, including cancers of the spleen, as well as cancers of other tissues where expression has been observed. Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 975 of SEQ ID NO:20, b is an integer of 15 to 989, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 11**

It has been discovered that this gene is expressed primarily in cells of the immune system, including monocytes and neutrophils.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders affecting the immune

system, such as AIDS. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 118 as residues: Ser-12 to Asp-20, Gly-22 to Gly-32, Ala-49 to Thr-57.

The tissue distribution in monocytes and neutrophils indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune system disorders, including AIDS. Furthermore, expression of this gene product in monocytes and neutrophils suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in monocytes and neutrophils also strongly suggests a role for this protein in immune function and immune surveillance. Protein,

as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 481 of SEQ ID NO:21, b is an integer of 15 to 495, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

## 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 12**

It has been discovered that this gene is expressed primarily in cells of the immune system, including monocytes.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders affecting the immune system. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 119 as residues: Glu-35 to Trp-42.



The tissue distribution suggests that the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in monocytes suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all  
5 hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as  
10 well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have  
15 commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in monocytes also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or  
20 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
25 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2303 of SEQ ID NO:22, b is an integer of 15 to 2317, where both a and b correspond to the positions of  
30 nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 13**

It has been discovered that this gene is expressed primarily in cells of the immune system, including monocytes.

5           Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of the immune system. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell  
10           type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene  
15           expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

          The tissue distribution in monocytes indicates that the protein products of this clone are useful for the diagnosis and/or treatment of disorders of the immune system. Expression of this gene product in monocytes suggests a role in the regulation of the  
20           proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

25           Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory  
30           bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of

various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in monocytes also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1712 of SEQ ID NO:23, b is an integer of 15 to 1726, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 14**

The translation product of this gene shares sequence homology with a gene from *C. elegans* of unknown function.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: TRPITYVLLAG (SEQ ID NO:224). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 11.

It has been discovered that this gene is expressed primarily in fetal lung, liver, spleen and heart tissues, as well as adult liver, bladder, endometrial stromal cells, synovium, colon cancer, smooth muscle, keratinocytes, and the bone marrow derived cell line RS4;11.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of the musculo-skeletal system, and cancers of the immune system. Similarly, polypeptides and antibodies  
5 directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the musculo-skeletal and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, musculo-skeletal, cancerous and wounded  
10 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in tissues of the immune system indicates that the  
15 protein products of this clone are useful for treating proliferative disorders of immune system precursor cells. Alternatively, the tissue distribution in smooth muscle and heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound  
20 healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of  
25 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 515 of SEQ ID NO:24, b  
30 is an integer of 15 to 529, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 15

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: GTSLTAPLLEFLLALYFLFADAMQLNDKWQGLCWP (SEQ ID NO:225). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 It has been discovered that this gene is expressed primarily in T-cells, fetal spleen and infant brain tissues, and to a lesser extent in many other tissues including melanocytes, lung cancer, macrophages, dendritic cells, stromal cells, adrenal gland and others.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
15 diagnosis of the following diseases and conditions: inflammation and autoimmunity, developing tissues. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developing system, expression of this gene at  
20 significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

25 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 122 as residues: Ser-46 to Gly-51.

The tissue distribution in T-cells and other immune cells indicates that the protein products of this clone are useful for treating diseases involving the activation of T-cells, including inflammation and autoimmune diseases. Alternatively, the tissue  
30 distribution in a wide range of fetal tissues suggests that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and

treatment of cancer and other proliferative disorders. Similarly, fetal development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1741 of SEQ ID NO:25, b is an integer of 15 to 1755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 16**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: LANFZCSDCAQTVLFLVLFZILVFTYEIPF (SEQ ID NO:226). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 13. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 13. Recently another group published this gene, referring to it as CLN5 (See Genbank Accession No.: 3342386).

It has been discovered that this gene is expressed primarily in placental tissue, 12 week embryos, and tumors including testes, tongue and pharynx, and to a lesser extent in adipose tissue, tonsils, melanocytes, fetal spleen, macrophages, T-cells, amniotic cells, and brain tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: tumors, particularly of the tongue and throat, and neurodegenerative disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and digestive systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., tongue, throat, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 123 as residues: Pro-44 to Ala-60, Val-187 to Thr-193, Lys-203 to Ala-210, Thr-212 to Cys-219.

The tissue distribution in tongue and pharynx carcinoma tissue indicates that the protein products of this clone are useful for diagnosing and/or treating oral cancers, including tumors of the throat and tongue. Furthermore, the tissue distribution in brain tissue suggests that the protein product of this clone is useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as neuronal ceroid lipofuscinoses (NCLs), Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1737 of SEQ ID NO:26, b is an integer of 15 to 1751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 17**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences:

QAWHEVGGGVRRRCWFVLGERRAGSLLSASYGTFAMPG

MVLFGRRWAIASDDLVPFGFFELVVRVLWWIGILTLYL (SEQ ID NO:227),  
and/or PGMVLFGRRWAIASDDLVPFGFFELVVRVLWWIGILTLYLMHRGKLD  
CAGGALLSSYLIVLMILLAVVICTVSAIMCVSMRGTCNPGPRKSMKLLYIRL  
ALFFPEMVWASLGAAWVADGVQCD (SEQ ID NO:228). Polynucleotides  
encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed in activated neutrophils, infant brain tissue and primary dendritic cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of the immune system, and neurodegenerative disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and neural systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual



having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 124 as residues: Pro-47 to Met-53, Ser-130 to Ser-138.

5       The tissue distribution in neutrophils and primary dendritic cells indicates that the protein products of this clone are useful for diagnosing and/or treating immune system disorders. Expression of this gene product in neutrophils and primary dendritic cells suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem  
10 cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
15 and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of  
20 various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in neutrophils and primary dendritic cells also strongly suggests a role for this protein in immune function and immune surveillance.

Alternatively, the tissue distribution in brain tissue suggests that the protein product of this clone is useful for the detection/treatment of neurodegenerative  
25 disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play  
30 a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies

directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1198 of SEQ ID NO:27, b is an integer of 15 to 1212, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 18**

It has been discovered that this gene is expressed primarily in neutrophils, and to a lesser extent in other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and inflammatory disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 125 as residues: Gln-17 to Ser-24.

The tissue distribution in neutrophils indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune and inflammatory disorders. Expression of this gene product in neutrophils suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of  
5 potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as  
10 well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have  
15 commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in neutrophils also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or  
20 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
25 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1098 of SEQ ID NO:28, b is an integer of 15 to 1112, where both a and b correspond to the positions of  
30 nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 19**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: HERNCFPMWLNHSAFPPV (SEQ ID NO:229).

- 5 Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in neutrophils, and to a lesser extent in other tissues.

- Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
10 diagnosis of the following diseases and conditions: immune and inflammatory disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels  
15 may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

- 20 The tissue distribution in neutrophils indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune and inflammatory disorders. Expression of this gene product in neutrophils suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene  
25 product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

- Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker  
30 and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune

deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of this gene product in neutrophils also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 734 of SEQ ID NO:29, b is an integer of 15 to 748, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

20

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 20**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: GWTRENDHRALSKAGIGSAEIQPSNLRVGS AKDLGKPW AGKLLLLSSCLLFFSLGVLYRGQMLAPPLQEDWKGGVKDSDLIDDSSASPIPP SYLEYKAALYPFSEHKSVRNATDSLTFVLVTDHFLDNQDSQ (SEQ ID NO:230), GWTRENDHRALSKAGIGSAEIQPSNLRVGS AKDLGKPWAGKLLLL (SEQ ID NO:231), SSCLLFFSLGVLYRGQMLAPPLQEDWKGGVKDSDLIDDSSASPIPP (SEQ ID NO:232), and/or SYLEYKAALYPFSEHKSVRNATDSLTFVLVTDHFL DNQDSQ (SEQ ID NO:233). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in ovarian cancer tissue, and to a lesser extent in other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: ovarian cancer. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the ovaries, expression of this gene at significantly higher or lower levels may be detected in  
10 certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 127 as residues: Thr-20 to Gly-27, Gly-32 to Phe-41.

The tissue distribution in ovarian cancer tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of ovarian cancer, as well as cancers of other tissues where expression has been observed. Protein, as  
20 well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of  
25 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 764 of SEQ ID NO:30, b  
30 is an integer of 15 to 778, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 21

5           When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent other cells, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The  
10   Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

          In specific embodiments, polypeptides of the invention comprise the following  
15   amino acid sequences: LKFHQESLSGD (SEQ ID NO:234). Polynucleotides encoding these polypeptides are also encompassed by the invention.

          It has been discovered that this gene is expressed primarily in fast-growing tissues such as immune/hematopoietic tissues, early developmental stage human tissues, and tumor tissues, and to a lesser extent in some other tissues.

20           Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: growth disorders, immune and inflammatory diseases, and tumorigenesis. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for  
25   differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune/hematopoietic system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an  
30   individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 128 as residues: Glu-60 to Arg-65.

The tissue distribution in immune tissues, in conjunction with the biological activity data, indicates that the protein products of this clone are useful for the diagnosis and/or treatment of growth disorders, immune and inflammatory diseases, and tumorigenesis. Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells suggests that this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1310 of SEQ ID NO:31, b is an integer of 15 to 1324, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 22**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: EAKSRPVTQAGVQWHDLGSLQPLPP (SEQ ID NO:235).

Polynucleotides encoding these polypeptides are also encompassed by the invention.



It has been discovered that this gene is expressed primarily in ovarian cancer tissue, and to a lesser extent in fetal liver/spleen and retinal tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: ovarian cancer, immune disorders, and retinal disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the ovaries, immune and ocular systems, expression of this gene at  
10 significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, ovaries, retina, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 The tissue distribution in ovarian cancer tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of ovarian cancer, as well as cancers of other tissues where expression has been observed. The tissue distribution also suggests that the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this  
20 gene product in fetal liver/spleen suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune  
25 responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune  
30 deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have

commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in retinal tissue suggests that the protein product of this clone is useful for the treatment and/or detection of eye disorders including blindness, color blindness, impaired vision, short and long sightedness, retinitis pigmentosa, retinitis proliferans, and retinoblastoma, retinoblastoma, retinopathy and retinoschisis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 725 of SEQ ID NO:32, b is an integer of 15 to 739, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 23

The translation product of this gene shares sequence homology with a *C. elegans* protein of unknown function (See Genbank Accession No.: gnllPID1348017). When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates fibroblast cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. The gene encoding the disclosed cDNA is thought to reside on

chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: EAKSRPVTQAGVQWHDLGSLQPLPP (SEQ ID NO:236),  
5 and/or ALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPSELELDDVVIT  
NPHIEAILENEDWIEDASGLMSHCIAILKICHTLTEKLVAMTMGSGAKMKTSA  
SVSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDAR (SEQ ID NO:237).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in fast growing  
10 tissues such as early development stage human tissues, immune/hematopoietic  
tissues, melanocytes, and tumor tissues, and to a lesser extent in some other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential  
identification of the tissue(s) or cell type(s) present in a biological sample and for  
diagnosis of the following diseases and conditions: growth disorders, immune and  
15 inflammatory disorders, skin and connective tissue disorders, and tumorigenesis.  
Similarly, polypeptides and antibodies directed to those polypeptides are useful to  
provide immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the fast  
growing tissues such as early development stage human tissues,  
20 immune/hematopoietic tissues, skin and connective tissue, and tumor tissues,  
expression of this gene at significantly higher or lower levels may be detected in  
certain tissues or cell types (e.g., musculo-skeletal, skin, immune, developing,  
cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
synovial fluid or spinal fluid) taken from an individual having such a disorder,  
25 relative to the standard gene expression level, i.e., the expression level in healthy  
tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
130 as residues: Pro-34 to Ser-43, Glu-54 to Ser-60.

The tissue distribution suggests that the protein product of this clone is useful  
30 for the diagnosis and/or treatment of growth disorders, immune and inflammatory  
disorders, and tumorigenesis. Alternatively, the tissue distribution in melanocytes, in

conjunction with the observed biological activity data, suggests that the protein product of this clone is useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. 5 keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, 10 pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma.

Moreover, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, 15 and ringworm). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are 20 related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the 25 general formula of a-b, where a is any integer between 1 to 1448 of SEQ ID NO:33, b is an integer of 15 to 1462, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 24**

When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent other cells, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences:

DVESRGPSARCLPVVPGSLLPGLEPATKLM PGGLAPGHG  
 APVRELLLPLLSQPTLGSLWDSLRHCSLLCNPLSCVPALEAPPSLVSLGCSGGC  
 15 PRLSLAGSASFPFLTALLSLLNTLAQIHKGLCGQLAAILAAPGLQNYFLQCVA  
 PGAAPHLTPFSAWALRHEYHLQYLALALAQAALQPLPATHAALYHGMAL  
 ALLSRLLPGSEYLTHELLSCVFRLEFLPERTSGGPEAADFSDQLSLGSSRVPR  
 CGQGTLAQAQCDLPSIRNCYLTHCSPARASLLASQALHRGELQRVPTLLLP  
 MPTPELLPTDWPFLH (SEQ ID NO:238),  
 20 DVESRGPSARCLPVVPGSLLPGLEPATKLM PGGLAPGHGAPVRE (SEQ ID  
 NO:239), LLLPLLSQPTLGSLWDSLRHCSLLCNPLSCVPALEAPPSLVSLGC  
 (SEQ ID NO:240), SGGCPRLSLAGSASFPFLTALL  
 SLLNTLAQIHKGLCGQLAAILA (SEQ ID NO:241), APGLQNYFLQCVAPGAAP  
 HLTPFSAWALRHEYHLQYLALALAQA (SEQ ID NO:242), AAALQPLPATHAA  
 25 LYHGMALALLSRLLPGSEYLTHELLSCVFR (SEQ ID NO:243), LEFLPERTSG  
 GPEAADFSDQLSLGSSRVPRCGQGTLAQAQCDL (SEQ ID NO:244), and/or  
 PSIRNCYLTHCSPARASLLASQALHRGELQRVPTLLLPMPTEPELLPTDWPFLH  
 (SEQ ID NO:245). Polynucleotides encoding these polypeptides are also  
 encompassed by the invention.

It has been discovered that this gene is expressed primarily in hematopoietic tissues and fetal heart tissue, and to a lesser extent in brain and gall bladder tissues, and some other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential  
5 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and inflammatory disorders, cardiovascular disorders, and growth disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
10 of the above tissues or cells, particularly of the hematopoietic and vascular systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., vascular, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene  
15 expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 131 as residues: Tyr-88 to Trp-102, Asp-105 to Ser-110.

The tissue distribution in hematopoietic tissues, in conjunction with the  
20 observed biological activity data, indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune and inflammatory disorders and growth disorders. Alternatively, the tissue distribution in fetal heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease,  
25 restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
30 related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2801 of SEQ ID NO:34, b  
5 is an integer of 15 to 2815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

### FEATURES OF PROTEIN ENCODED BY GENE NO: 25

10 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: VGSVLGAFLTFPGLRLAQTHRDALT (SEQ ID NO:246). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 19. Accordingly, polynucleotides related to this invention are useful as a marker in  
15 linkage analysis for chromosome 19.

It has been discovered that this gene is expressed primarily in human pituitary tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
20 diagnosis of the following diseases and conditions: hyperpituitarism and hypopituitarism. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or  
25 lower levels may be detected in certain tissues or cell types (e.g., endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. This gene is found on the short arm  
30 of chromosome 19 and, therefore, is useful as a chromosome marker.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 132 as residues: Met-1 to Pro-6, Gln-89 to Ala-94, Pro-161 to Cys-173.

The tissue distribution in pituitary tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of pituitary disorders. More generally, the tissue distribution in pituitary tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1064 of SEQ ID NO:35, b is an integer of 15 to 1078, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

## **25 FEATURES OF PROTEIN ENCODED BY GENE NO: 26**

It has been discovered that this gene is expressed highly and specifically in placental and bone marrow cDNA libraries, and to a lesser extent in T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune, developmental and reproductive disorders. Similarly, polypeptides and antibodies directed to those



polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developing systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, developmental, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

10           The tissue distribution in bone marrow and placental tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of immune and reproductive disorders. The tissue distribution in bone marrow suggests that the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

          Alternatively, the tissue distribution in placental tissue suggests that the protein product of this clone is useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta suggests that this gene product may play a role in the proper establishment and maintenance of placental function. Alternately, this gene product may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus.

          Expression of this gene product in a vascular-rich tissue such as the placenta also suggests that this gene product may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in

vascular function, such as in angiogenesis. It may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as,  
5 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of  
10 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1203 of SEQ ID NO:36, b  
15 is an integer of 15 to 1217, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 27**

20 In specific embodiments, polypeptides of the invention comprise the following amino acid sequences:

LECTDTIMVHCSLKLLSPSDXSHSASQVAKTRGVHHXTQ

LIFKVFFVXMGSHSTKYXSIRPGLLP (SEQ ID NO:247). Polynucleotides encoding these polypeptides are also encompassed by the invention.

25 It has been discovered that this gene is expressed primarily in human prostate and smooth muscle tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders in the prostate gland,  
30 vascular and connective tissues. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive and urinary system and vascular system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, vascular, cancerous and wounded  
5 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in prostate and smooth muscle tissues indicates that the  
10 protein products of this clone are useful for the diagnosis and/or treatment of prostate gland, vascular and connective tissue disorders. The tissue distribution in smooth muscle tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound  
15 healing. The expression in the prostate tissue may indicate the gene or its products can be used in the disorders of the prostate, including inflammatory disorders, such as chronic prostatitis, granulomatous prostatitis and malacoplakia, prostatic hyperplasia and prostate neoplastic disorders, including adenocarcinoma, transitional cell carcinomas, ductal carcinomas, squamous cell carcinomas, or as hormones or factors  
20 with systemic or reproductive functions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25 related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
30 general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:37, b is an integer of 15 to 1282, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 28**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: ESSFVPPAAHSSLC (SEQ ID NO:248). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 It has been discovered that this gene is expressed primarily in human pituitary tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: hyperpituitarism and  
10 hypopituitarism. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., endocrine,  
15 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in pituitary tissue indicates that the protein products of  
20 this clone are useful for the diagnosis and/or treatment of pituitary gland disorders such as hypopituitarism and hyperpituitarism. More generally, the tissue distribution in pituitary tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of  
25 the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism) , hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 545 of SEQ ID NO:38, b is an integer of 15 to 559, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 29

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences:

LLPGQQEATQCVEAGAGEGALTPMCPCRQEQFVDLYKEF

EPSLVNSTVYIMAMAIQMAPFAINYKVRPGPCXNIHCLPTQPHPMKPSVPHPH  
RARPSWRACPRTSPWCGVWQFHSWPSLACSSAPRPTSTASLASWTSLWSSS

WSLPRSCSWTSAWRSWPTASCSSSWGPRS (SEQ ID NO:249),  
LLPGQQEATQCV EAGAGEGALTPMCPCRQEQFVDLYKEFEPSTLVN (SEQ ID  
NO:250), STVYIMAMAIQMAPFAINYKVRPGPCXNIHCLPTQPHPMKPSVP

(SEQ ID NO:251),  
HHRARPSWRACPRTSPWCGVWQFHSWPSLACSSAPRPTSTA (SEQ ID  
NO:252), and/or SLASWTSLWSSSWSLPRSCSWTSAWRSWPTASCSSSWG PRS  
(SEQ ID NO:253). Polynucleotides encoding these polypeptides are also  
encompassed by the invention.

It has been discovered that this gene is expressed primarily in human pituitary and breast tissues, and to a lesser extent in endometrial and ovarian cancer tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: hyperpituitarism and hypopituitarism, and cancers of the female reproductive system. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and reproductive systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., endocrine, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 136 as residues: Ser-3 to Lys-8.

The tissue distribution in pituitary tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of disorders in the pituitary gland. More generally, the tissue distribution in pituitary tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Alternatively, the tissue distribution in breast tissue and cancerous tissues of the endometrium and ovaries suggests that the translation product of this gene is useful for the detection and/or treatment of disorders and cancers of the female reproductive system, as well as cancers of other tissues where expression has been observed. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 789 of SEQ ID NO:39, b is an integer of 15 to 803, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

5

### FEATURES OF PROTEIN ENCODED BY GENE NO: 30

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: TRNLSFIKCVIHNFWIPKESNEITIINPYRETVCFVSVEPVKKIFNY (SEQ ID NO:254). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10

It has been discovered that this gene is expressed primarily in human synovial sarcoma tissue.

15

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., skeletal, connective, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

20

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 137 as residues: Thr-29 to Pro-34.

25

The tissue distribution in synovial sarcoma tissue indicates that the protein products of this clone are useful for the diagnosis and/or treatment of diseases of the synovium. In addition, the

30

Expression of this gene product in synovium suggests a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma,



tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial arthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1496 of SEQ ID NO:40, b is an integer of 15 to 1510, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

## 20 **FEATURES OF PROTEIN ENCODED BY GENE NO: 31**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: LVVLFASSNSRYLK YFFLVPLILGSAW (SEQ ID NO:255). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in human rhabdomyosarcoma and fetal liver/spleen tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: malignant neoplasms and hematopoiesis. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the skeletal and immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., musculo-skeletal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 138 as residues: Gly-29 to Thr-35.

The tissue distribution in rhabdomyosarcoma and fetal liver/spleen tissues indicates that the protein products of this clone are useful for diagnosis and treatment of skeletal and immune disorders. The expression in rhabdomyosarcoma tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various muscle disorders, such as muscular dystrophy, cardiomyopathy, fibroids, myomas, and rhabdomyosarcomas. Alternatively,

Expression of this gene product in fetal liver/spleen tissue suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
5 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1081 of SEQ ID NO:41, b is an integer of 15 to 1095, where both a and b correspond to the positions of  
10 nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 32**

It has been discovered that this gene is expressed primarily in fibrosarcoma  
15 tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: fibrosarcoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide  
20 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the connective tissue system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., musculo-skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or  
25 spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 139 as residues: Ser-34 to Gln-40, Gly-42 to Glu-48, Tyr-56 to Leu-62.

30 The tissue distribution in only fibrosarcoma tissue suggests that the protein product of this clone is useful for the treatment, diagnosis and/or prognosis of

fibrosarcoma's or other disorders related with fibrous tissue including fibroma, fibromatosis, fibromyoma, fibromyositis, fibrosis and fibrositis. Likewise, the expression in fibrosarcoma tissue suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various muscle disorders, such as muscular dystrophy, cardiomyopathy, myomas, and rhabdomyosarcomas. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1148 of SEQ ID NO:42, b is an integer of 15 to 1162, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

## **20 FEATURES OF PROTEIN ENCODED BY GENE NO: 33**

It has been discovered that this gene is expressed primarily in Hodgkins lymphoma and breast cancer tissues, and to a lesser extent in stromal cells and brain tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: lymphoma, breast cancer, and neurological disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and nervous systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types

(e.g., immune, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

5 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 140 as residues: Pro-22 to Lys-29.

The tissue distribution in Hodgkins lymphoma, brain and breast cancer tissues suggests a role in the treatment, diagnosis and/or prognosis of breast cancer, immune and hematopoietic disorders including arthritis, asthma, immunodeficiency diseases, 10 leukemia and Hodgkin's lymphoma and neurodegenerative disease states and behavioral disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed 15 tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically 20 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:43, b is an integer of 15 to 657, where both a and b correspond to the positions of 25 nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 34**

In specific embodiments, polypeptides of the invention comprise the following 30 amino acid sequences: HEWKCKQKYSESGNTRIGN (SEQ ID NO:256). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in chronic synovitis tissue, and to a lesser extent in fetal kidney and testes tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: synovitis, renal disorders and male infertility. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the connective tissue system, the renal system, and the male reproductive system,  
10 expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., skeletal, renal, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not  
15 having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 141 as residues: Met-33 to Pro-39, Ser-74 to Trp-79.

The tissue distribution of this gene in chronic synovitis, testes, and kidneys suggests a role in the treatment, diagnosis and prognosis of synovial membrane  
20 disorders including synovitis, renal disorders including kidney failure, renal colic, renal diabetes, hypertension, osteodystrophy, tubular acidosis and kidney stones; and and male infertility. Furthermore, the tissue distribution in testes tissue indicates that the protein product of this clone is useful for the treatment and/or diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm  
25 maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene  
30 expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific

tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. In addition, the

Expression of this gene product in synovium suggests a role in the detection  
5 and/or treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and  
10 specific joint abnormalities as well as chondrodysplasias (ie. spondyloepiphyseal dysplasia congenita, familial arthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence  
20 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1141 of SEQ ID NO:44, b is an integer of 15 to 1155, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a  
25 + 14.

### **FEATURES OF PROTEIN ENCODED BY GENE NO: 35**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: LLPLCFLGPRQVLEEFPSIV (SEQ ID NO:257).

30 Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in brain tissue, and to a lesser extent in osteoclastoma and testes tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: neurological disorders and male reproductive disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system and the male reproductive system, expression of  
10 this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 The tissue distribution of this gene in brain tissue suggests a role in the diagnosis, prognosis and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder and panic disorder. In addition, the gene or gene product may also play a role in the  
20 treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
25 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
30 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1098 of SEQ ID NO:45, b



is an integer of 15 to 1112, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 36

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: PTRPSKHQEAGS (SEQ ID NO:258). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly,  
10 polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

It has been discovered that this gene is expressed primarily in adult and fetal heart tissue, and to a lesser extent in fetal lung and fetal liver/spleen tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential  
15 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: cardiovascular and immune disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
20 the vascular and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., vascular, immune, pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in  
25 healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 143 as residues: Val-2 to Ser-14.

The tissue distribution in heart, fetal liver and fetal spleen tissues suggests a role in the treatment and/or diagnosis of cardiovascular disorders including  
30 myocardial infarction, congestive heart failure, coronary failure, as well as immune disorders including autoimmune diseases, such as lupus, transplant rejection, allergic

reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS.

Furthermore, the tissue distribution in adult and fetal heart tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4009 of SEQ ID NO:46, b is an integer of 15 to 4023, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

## **20 FEATURES OF PROTEIN ENCODED BY GENE NO: 37**

It has been discovered that this gene is expressed primarily in testes tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: male infertility and reproductive disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the male reproductive system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the

standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in testes tissues suggests a role in the treatment and/or diagnosis of male infertility, and testicular disorders including cancer. Furthermore, the tissue distribution in testes tissue indicates that the protein product of this clone is useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 528 of SEQ ID NO:47, b is an integer of 15 to 542, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

**FEATURES OF PROTEIN ENCODED BY GENE NO: 38**

It has been discovered that this gene is expressed primarily in apoptotic T-cells, and to a lesser extent in brain tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential  
5 identification of the tissue(s) or cell type(s) present in a biological sample and for  
diagnosis of the following diseases and conditions: immune and neurological  
disorders. Similarly, polypeptides and antibodies directed to those polypeptides are  
useful to provide immunological probes for differential identification of the tissue(s)  
or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
10 the immune and nervous systems, expression of this gene at significantly higher or  
lower levels may be detected in certain tissues or cell types (e.g., immune, neural,  
cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,  
synovial fluid or spinal fluid) taken from an individual having such a disorder,  
relative to the standard gene expression level, i.e., the expression level in healthy  
15 tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
145 as residues: Glu-33 to Tyr-42.

The tissue distribution in apoptotic T-cells suggests potential roles in the  
treatment and/or diagnosis of immune disorders including of immune and  
20 autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis,  
asthma, immunodeficiency diseases, leukemia, and AIDS. Alternatively, expression  
in brain tissue suggests a role in the treatment and/or diagnosis of neurodegenerative  
disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's  
Disease, Huntington's Disease, schizophrenia, mania, dementia, paranoia, obsessive  
25 compulsive disorder and panic disorder. Furthermore, the tissue distribution in  
apoptotic T-cells indicates that the translation product of this gene may also be  
involved in apoptosis or tissue differentiation and could again be useful in cancer  
therapy. Protein, as well as, antibodies directed against the protein may show utility as  
a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly  
available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1481 of SEQ ID NO:48, b is an integer of 15 to 1495, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 39**

The translation product of this gene shares sequence homology with phosphomannomutase, which is thought to be important in mannose metabolism.

It has been discovered that this gene is expressed primarily in meningioma and testis tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: meningioma related diseases. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 146 as residues: Ser-33 to Lys-43.

The tissue distribution in meningioma, and the homology to phosphomannomutase, suggests that the protein product of this clone is useful for the

diagnosis and/or intervention of meningioma related diseases. For example, the gene product can be used for preventing microbial infection of the meninges, for imaging conjugates, or as a secretory factor as a endocrine with systemic, central or peripheral nerve functions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 804 of SEQ ID NO:49, b is an integer of 15 to 818, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 40**

It has been discovered that this gene is expressed primarily in tonsils, osteoclastoma and retinoic acid treated teratocarcinoma cells, and to a lesser extent in macrophages, female bladder, adipose tissue, myeloid progenitor cells, prostate tissue, and number of other tissues and organs.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: tonsils and osteoclast related diseases. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and bone systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
5 147 as residues: Glu-55 to Arg-61, Gln-84 to Ser-92, Ser-99 to Ser-104.

The tissue distribution in tonsils and osteoclastoma suggests that the protein product of this clone is useful for the diagnosis and/or intervention of diseases related to tonsils or osteoclasts. For example, tonsillitis, adenoids, peritonsillar abscess, neoplasms, or bone related disorders like rickets, abnormalities of bone growth and  
10 modelling, fracture, osteonecrosis, and osteoporosis etc. Expression of this gene product in osteoclastoma suggests that it may play a role in the survival, proliferation, and/or growth of osteoclasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis.

Alternatively, the expression of this gene product in tonsils suggests a role in  
15 the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

20 Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory  
25 bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1697 of SEQ ID NO:50, b is an integer of 15 to 1711, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 41**

It has been discovered that this gene is expressed primarily in resting T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: T-cell related disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in resting T-cells suggests that the protein product of this clone is useful for the diagnosis and/or intervention of T-cell related disorders, such as infection, inflammation, allergy, tissue/organ transplantation, immune deficiency etc. Furthermore, the expression of this gene product in T cells also strongly suggests a role for this protein in immune function and immune surveillance. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.



Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 735 of SEQ ID NO:51, b is an integer of 15 to 749, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 42

The translation product of this gene shares weak sequence homology with Human metastasis suppressor KiSS-1 fragment, which is thought to be important in the diagnosis, prevention, staging and/or treatment of cancers, such as melanoma (See Accession No. W15789).

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: GQGPAGRWVRRLPCSR RAGGERGPHWGVWAGPQM SCGLXFGP (SEQ ID NO:259), WRTQGPMVLLWVVTCPATMLTEPQNPHLIGF VAYSGPSHTTQPHKYWLLLDGQADPAAAE GPVKRKAASV VWWPQALRHLS LLVHCWEESYEMNIGCQSLWAGGLASSGNGWDLGVAFR RDTCMSSSSLHW KEFKYAPGSLHYFALS FVLILTEICLVSSGMGFPQEGKHFSVLGSPDCSLWGR DEHVPREFA (SEQ ID NO:260), WRTQGPMVLLWVVTCPATMLTEPQNPHLIGFVAY SGPSHTTQ (SEQ ID NO:261), PHKYWLLLDGQADPAAAE GPVKRKAASV VWW PQALRHLSLL (SEQ ID NO:262), VHCWEESYEMNIGCQSLWAGGLASSGNGW DLGVAFR RDTCM (SEQ ID NO:263), SSSSLHWKEFKYAPGSLHYFALS FVLILT EICLVSSGMGFPQEG (SEQ ID NO:264), and/or KHFSVLGSPDCSLWGRDEHV PREFA (SEQ ID NO:265). Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

It has been discovered that this gene is expressed primarily in tonsils,  
5 osteoclastoma and teratocarcinoma tissues, and to a lesser extent in female bladder, adipose tissue, myeloid progenitor, prostate tissue, and number of other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: diseases related to tonsils and  
10 osteoclasts. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and bone system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, skeletal,  
15 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in tonsils and osteoclastoma tissues suggests that the  
20 protein product of this clone is useful for the diagnosis and/or treatment of diseases related to tonsils and osteoclasts. For example, tonsillitis, adenoids, peritonsillar abscess, neoplasms, or abnormal growth and modelling of the bone, osteonecrosis, osteoporosis, osteodystrophy, osteoclastoma etc. Expression of this gene product in osteoclastoma suggests that it may play a role in the survival, proliferation, and/or  
25 growth of osteoclasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis.

Moreover, the expression of this gene product in tonsils suggests a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene  
30 product may be involved in the regulation of cytokine production, antigen

presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1077 of SEQ ID NO:52, b is an integer of 15 to 1091, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

## 25 **FEATURES OF PROTEIN ENCODED BY GENE NO: 43**

The translation product of this gene shares sequence homology with the *Drosophila* gene "maleless", which is one of four known regulatory loci required for increased transcription (dosage compensation) of X-linked genes (See Genbank Accession No.: gil157906).

30 It has been discovered that this gene is expressed primarily in normal prostate tissue, testes tissue, whole 6-week old embryonic tissue, human colon carcinoma

(HCC) cell line, and cerebellum tissue, and to a lesser extent in primary breast cancer, activated T-cells, and many other tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: diseases of the prostate or colon, or male reproductive disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate or colon carcinoma, and male reproductive  
10 disorders, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., colon, prostate, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an  
15 individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 150 as residues: Val-39 to Ala-45.

The tissue distribution in colon and prostate tissues suggests that the protein product of this clone is useful for the diagnosis and/or treatment of prostate disorders  
20 such as prostatitis, prostatic hyperplasia, prostate cancers, or human colon carcinoma, as well as cancers of other tissues where expression has been observed. Alternatively, the tissue distribution in testes tissue, in conjunction with the homology to the *Drosophila* maleless gene, suggests that the translation product of this gene is useful for the detection and/or treatment of disorders involving the testes or the transcription  
25 of X-linked genes. Furthermore, the tissue distribution indicates that the protein product of this clone is useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence.

30 This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the

protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2240 of SEQ ID NO:53, b is an integer of 15 to 2254, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 44**

The translation product of this gene shares weak sequence homology with Eimeria antigen Eam45 M3, which is thought to be important in uses as a vaccine for protecting chickens against coccidiosis.

It has been discovered that this gene is expressed primarily in adrenal gland tissue, and to a lesser extent in activated T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: adrenal cortical insufficiency, adrenal cortical hyperfunction, neoplasia. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for

differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in adrenal gland tissue suggests that the protein product of this clone is useful for the diagnosis and/or intervention of disorders caused by adrenal gland abnormalities, such as adrenal cortical insufficiency, adrenal cortical hyperfunction, and neoplasia. More generally, the tissue distribution suggests that the protein product of this clone is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 472 of SEQ ID NO:54, b is an integer of 15 to 486, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 45**

The translation product of this gene shares sequence homology with neural thread protein, tumor necrosis factor related gene product, human alpha-1C2 adrenalin receptor, which is thought to be important for diagnosing the presence of Alzheimer's disease, neuroectodermal tumours and a malignant astrocytoma, or  
5 diagnosis of hepatocellular carcinomas and preneoplastic or pathological conditions of the liver, and tumor immunity.

It has been discovered that this gene is expressed primarily in activated T-cells and endothelial cells.

Therefore, nucleic acids of the invention are useful as reagents for differential  
10 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: Alzheimer's disease, neuroectodermal tumours and a malignant astrocytoma, hepatocellular carcinomas and tumors of various origins. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification  
15 of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and endothelial cells, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, endothelial, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual  
20 having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 152 as residues: Arg-38 to Arg-47.

The tissue distribution in immune and endothelial tissues, and the homology to  
25 neural thread protein, tumor necrosis factor related gene product, human alpha-1C2 adrenalin receptor, or Smaller hepatocellular oncoprotein (hhcm) gene product suggests that the protein product of this clone is useful for the diagnosis and/or treatment of tumors of various origins, including neuroectodermal tumours and a malignant astrocytoma, hepatocellular carcinomas, as well as syndromes inflicted by  
30 these cancers. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1256 of SEQ ID NO:55, b is an integer of 15 to 1270, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 46**

It has been discovered that this gene is expressed primarily in tumor tissues such as hepatocellular tumor, hemangiopericytoma, chronic lymphocytic leukemia, and activated T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: tumors of various origins. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatocellular tumor, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., liver, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in hepatocellular tumors suggests that the protein product of this clone is useful for the diagnosis and/or targeting of hepatocellular carcinomas, preneoplastic or pathological conditions of the liver, Alzheimer's disease,



neuroectodermal tumours and malignant astrocytoma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2045 of SEQ ID NO:56, b is an integer of 15 to 2059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 47**

It has been discovered that this gene is expressed primarily in glioblastoma, ulcerative colitis, and hemangiopericytoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: glioblastoma, hemangiopericytoma and their inflicted disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain tissues, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 154 as residues: Pro-31 to Ala-37.

The tissue distribution suggests that the protein product of this clone would be useful for the diagnosis, targeting and/or treatment of tumors in the brain, such as glioblastoma and hemangiopericytoma. Additionally, the gene products can be useful agent for the diagnosis and treatment of ulcerative colitis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 854 of SEQ ID NO:57, b is an integer of 15 to 868, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 48**

It has been discovered that this gene is expressed primarily in bone marrow.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immunodeficiency, tumor necrosis, infection, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and other hematopoietic disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types

(e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

5 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 155 as residues: Thr-47 to Val-53.

The tissue distribution in bone marrow suggests that the protein product of this clone is useful for the diagnosis and/or treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immuno-  
10 suppressive conditions (transplantation) and hematopoietic disorders. In addition this gene product may be applicable in conditions of general microbial infection, inflammation or cancer. Furthermore, the tissue distribution in bone marrow suggests that the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia,  
15 thrombocytopenia or leukemia.

The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy,  
20 immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence  
30 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 972 of SEQ ID NO:58, b is an integer of 15 to 986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 49**

It has been discovered that this gene is expressed primarily in bone marrow.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
10 diagnosis of the following diseases and conditions: immunodeficiency, tumor necrosis, infection, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and other hematopoietic disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of  
15 the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in  
20 healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 156 as residues: Leu-40 to Cys-47.

The bone marrow tissue distribution suggests that the protein product of this clone would be useful for the diagnosis and treatment of immune disorders including:  
25 leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immunosuppressive conditions (transplantation) and hematopoietic disorders. In addition this gene product may be applicable in conditions of general microbial infection, inflammation or cancer. Furthermore, the tissue distribution in bone marrow suggests that the protein product of this clone is useful for the treatment and diagnosis of  
30 hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia.

The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 681 of SEQ ID NO:59, b is an integer of 15 to 695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 50**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: IAQGTVP LTKRGVQSSGPDYPEGTLTPLPRG (SEQ ID NO:266 and 267). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in dendritic cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune disorders and related conditions such as leukemias, lymphomas, inflammation, hematopoietic dysfunction,

arthritis and asthma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of dendritic cells. For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels  
5 may be detected in certain tissues or cell types (e.g., dendritic cells, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 157 as residues: Ser-25 to Phe-31, Lys-55 to Arg-61.

The tissue distribution in dendritic cells suggests that the protein product of this clone is useful for the diagnosis and/or treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immuno-  
15 suppressive conditions (transplantation) and hematopoietic disorders. In addition this gene product may be applicable in conditions of general microbial infection, inflammation or cancer.

Moreover, the expression of this gene product in dendritic cells also strongly suggests a role for this protein in immune function and immune surveillance. Protein,  
20 as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of  
25 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 300 of SEQ ID NO:60, b  
30 is an integer of 15 to 314, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 51

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DCLYLALSFPWHCHCHHHPPSGSLLYPF (SEQ ID NO:268). Polynucleotides encoding these polypeptides are also encompassed by the invention. The translation product of this gene shares sequence homology with a C. elegans protein of unknown function (See Genbank Accession No.: gil1947142  
10 (AF000264)).

It has been discovered that this gene is expressed primarily in healing abdominal wound tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
15 diagnosis of the following diseases and conditions: tissue necrosis, wound healing, ulceration, neoplasms or cancer. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of injured tissue, expression of this gene at significantly  
20 higher or lower levels may be detected in certain tissues or cell types (e.g., vascular, endothelial, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

25 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 158 as residues: Pro-34 to Tyr-43, Gln-73 to Cys-86, Pro-98 to Leu-103.

The tissue distribution in healing abdominal wound tissue suggests that the protein product of this clone is useful for the treatment and/or diagnosis of conditions involving tissue repair and wound healing. Tissue repair may be indicated in cases of  
30 injury to the skin or internal organs, ulceration, cellular necrosis or other conditions involving healing of both diseased or non-diseased, traumatized tissue. In addition,

because of the implications of tissue regeneration, remodeling and growth regulation, the protein product of this gene may have indications in the diagnosis and treatment of neoplasms and cancer.

More generally, the tissue distribution in endothelial tissue indicates that the protein product of this gene is useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Likewise, the tissue distribution further suggests that the protein product of this clone is useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this clone may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are



related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 720 of SEQ ID NO:61, b is an integer of 15 to 734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 52**

The translation product of this gene shares sequence homology with FAR-17A, which is an androgen induced protein, absent in castrated hamsters (See Genbank Accession No.: gil191315), as well as a male hormone-dependent gene product (See GenSeq Accession No.: R10612). The gene encoding the disclosed cDNA is thought to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequences: ASLPPSRSRPLANMALVPCQVLRMAILLSYCSILCNYKA IEMPSHQTYGGSWKFLTFIDLVIQAVFFGICVLTDLSSLLTRGSGNQEQERQLK KLISLRDW (SEQ ID NO:269). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in fetal liver and spleen tissue, and to a lesser extent in a variety of other fetal tissues and brain tissues.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune disorders including leukemias, lymphomas; reproductive and endocrine disorders, including testicular cancer; and liver disorders (e.g. hepatoblastoma, metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide

immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and reproductive systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 159 as residues; Thr-59 to Gly-70, Tyr-132 to Glu-150.

The tissue distribution and homology to FAR-17A suggests that the protein product of this clone is useful for the treatment and/or diagnosis of androgen related conditions and disorders. Male reproductive and endocrine disorders would be potential area of application (e.g. endocrine function, sperm maturation). It may also prove to be valuable in the diagnosis and treatment of testicular cancer.

More generally, the protein product of this clone may be useful for the treatment and/or diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1396 of SEQ ID NO:62, b is an integer of 15 to 1410, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 53**

Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of THP-1 to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of monocytes, and to a lesser extent, in immune or hematopoietic cells and tissues. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocytes.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: MSRSSRISGLSCPWLL (SEQ ID NO:270). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 1.

It has been discovered that this gene is expressed primarily in T-cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and hematopoietic diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells,

particularly of the immune and haemopoietic systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 160 as residues: Pro-42 to Cys-50, Leu-61 to Ala-66.

The tissue distribution in T-cells, combined with the detected calcium flux activity in monocytes suggests that the protein product of this clone would be useful for the treatment and diagnosis of immune and hematopoietic disorders. Moreover, the expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues.

Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1217 of SEQ ID NO:63, b is an integer of 15 to 1231, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

#### 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 54**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: DHWPAGFLPPAPGLKFPVALEVFRKVLPAVCPTDCSGS AGKERN (SEQ ID NO:271). Polynucleotides encoding these polypeptides are also encompassed by the invention.

20 It has been discovered that this gene is expressed primarily in liver.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: metabolic diseases and liver conditions. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., hepatic, liver, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder,

relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 161 as residues: Ser-31 to Gln-41.

5           The tissue distribution in liver suggests that the protein product of this clone would be useful for treatment and diagnosis of disorders of the metabolic system and liver disorders. Moreover, the protein product of this clone is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of  
10 hepatocyte progenitor cells). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
15 related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
20 general formula of a-b, where a is any integer between 1 to 598 of SEQ ID NO:64, b is an integer of 15 to 612, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

## 25   **FEATURES OF PROTEIN ENCODED BY GENE NO: 55**

When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response gene 1) promoter element. Thus, it is likely that this gene activates sensory neuron cells, and to a lesser extent in other neural cells and tissues, through the EGR1 signal transduction  
30 pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes

containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

It has been discovered that this gene is expressed primarily in T-cells and monocytes, and to a lesser extent in cancerous tissues, including cancerous colon  
5 tissue and placenta.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and haemopoietic disorders and cancer such as colon cancer, but also such cancers as breast cancer,  
10 cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, adenoma, and the like. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell  
15 type(s). For a number of disorders of the above tissues or cells, particularly of the immune and haemopoietic systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having  
20 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 162 as residues: Glu-63 to Trp-72.

The tissue distribution in T-cells and monocytes, combined with the detected  
25 EGR1 biological activity suggests that the protein product of this clone would be useful for treatment and diagnosis of disorders of the immune and haemopoietic systems and colon and other cancers. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

30 Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an

agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to  
5 transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues.

Moreover, the protein may represent a secreted factor that influences the  
10 differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression cellular sources marked by proliferating cells suggests this protein may play a role in the  
15 regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell  
20 death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate  
25 apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of



the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
5 general formula of a-b, where a is any integer between 1 to 2256 of SEQ ID NO:65, b is an integer of 15 to 2270, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

## 10 FEATURES OF PROTEIN ENCODED BY GENE NO: 56

The translation product of this gene has homology with several human keratin genes at the nucleotide level (see, for example, Troyanovsky, et al., Eur. J. Cell Biol. 59:127-137 (1992) which is hereby incorporated by reference herein). Based on the sequence similarity, the translation product of this clone is expected to share  
15 biological activities with keratin and growth factor proteins. Such activities are known in the art, and some of which are described elsewhere herein.

It has been discovered that this gene is expressed primarily in neutrophils.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
20 diagnosis of the following diseases and conditions: immune and haemopoietic disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and haemopoietic system, expression of this gene at significantly higher  
25 or lower levels may be detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

30 The tissue distribution in neutrophils suggests that the protein product of this clone would be useful for treatment and diagnosis of disorders of the immune and

haemopoietic system. Furthermore, sequence homology of the polynucleotides and polypeptides of the present invention with a number of human cytokeratin molecules, such as CK-8, CK-15, and CK-17, indicate that molecules of the present invention can be used diagnostically as markers of basal cell differentiation in complex epithelia and therefore indicative of a certain type of epithelial stem cells, as well as markers of the differentiation of other cell types such as neutrophils or other immune cells. Molecules of the present invention, or agonists or antagonists thereof, can also be used therapeutically to treat differentiation disorders of epithelial, neutrophil or other immune cell differentiation or activation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1269 of SEQ ID NO:66, b is an integer of 15 to 1283, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 57**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: EEIATSIEPIRDFLAIVFFASIGLHVFPPTFVAYELTVLVF LTLSVVV (SEQ ID NO:272). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in synovium, placenta, and stromal cells, and to a lesser extent in several other tissues and organs,

including, among others, bone marrow, palate, pituitary gland, and in tissue derived from osteosarcoma and chondrosarcoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: developmental disorders, as well as disorders of the musculoskeletal and haematopoietic systems, and cancers including especially osteosarcoma and chondrosarcoma, but also other cancers including breast cancer, colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer,  
10 stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, adenoma, and the like. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemopoietic and musculoskeletal  
15 systems, as well as developmental disorders, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., synovium, placenta, stromal, immune, hematopoietic, skeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene  
20 expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 164 as residues: Pro-81 to Ser-88.

The tissue distribution in placenta suggests that the protein product of this  
25 clone would be useful for treatment and diagnosis of developmental disorders. Polynucleotides and polypeptides of the present invention can be used diagnostically and therapeutically to detect and treat many cancers, particularly osteosarcoma and chondrosarcoma. In addition, the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the  
30 skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chrondomalacia and

inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial  
5 osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid).

Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Protein,  
10 as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of  
15 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1249 of SEQ ID NO:67, b  
20 is an integer of 15 to 1263, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 58**

25 Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of renal mesangial cells to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of renal and developing cells and tissues. Thus,  
30 polynucleotides and polypeptides have uses which include, but are not limited to, activating renal and developing cells and tissues.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: YCNLQCR (SEQ ID NO:273). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 It has been discovered that this gene is expressed primarily in the whole developing embryo, as well as in ovarian cancer and placenta.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: developmental or reproductive diseases and/or disorders, in addition to the following and ovarian cancer, as well as  
10 other cancers including breast cancer, colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, and the like. Similarly, polypeptides and antibodies directed to those polypeptides are useful to  
15 provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing and fetal system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph,  
20 amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in embryonic and ovarian tissue, combined with the detected calcium flux activity, suggests that the protein product of this clone would be  
25 useful for treatment and diagnosis of developmental disorders as well as ovarian and other cancers. Expression within embryonic tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving  
30 cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of

some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Therefore, the polynucleotides and polypeptides of the present invention are  
5 useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.  
Alternatively, the protein is useful in the detection, treatment, and/or prevention of  
10 vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
15 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
20 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1603 of SEQ ID NO:68, b is an integer of 15 to 1617, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

25

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 59**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SALIGNPKGCGFCFSPVVLREWSVESWKSRLRPFQAICK  
LKTNFR (SEQ ID NO:274). Polynucleotides encoding these polypeptides are also  
30 encompassed by the invention.

It has been discovered that this gene is expressed primarily in hypothalamus and anergic T cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: neurological and inflammatory defects, diseases, and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and immune systems, expression of  
10 this gene at significantly higher or lower levels may be detected in certain tissues (e.g., neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 166 as residues: His-33 to Trp-38.

The tissue distribution in hypothalamus and T-cells suggests that the protein product of this clone would be useful for study and treatment of immune and nervous system disorders. The protein product of this clone is useful for the detection,  
20 treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction,  
25 aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role  
30 in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal

differentiation or survival. Moreover, the expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1375 of SEQ ID NO:69, b



is an integer of 15 to 1389, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 60

The translation product of this gene shares nucleotide sequence homology with the human PKD1 gene which is thought to be important in polycystic kidney disease.

10 This gene is expressed widely with a predominant expression exhibited in liver, pediatric kidney, and in the whole 8 week old developing human embryo.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: cancer, growth, renal, and metabolic defects, diseases, and/or disorders. Similarly, polypeptides and antibodies  
15 directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine, digestive and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., renal, metabolic, hepatic, developmental,  
20 and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, bile, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in pediatric kidney suggests that the protein product of  
25 this clone would be useful for study and treatment of renal and general neoplasias and growth and development disorders. The protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and  
30 kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome.

Moreover, the expression within embryonic tissue suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders, particularly of the liver and other organs. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1882 of SEQ ID NO:70, b is an integer of 15 to 1896, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 61**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HEAALRGP (SEQ ID NO:275). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in human striatum depression.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: stroke, in addition to other, neurologically-related diseases and/or defects. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of  
10 this gene at significantly higher or lower levels may be detected in certain tissues (e.g., neural, musculoskeletal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 168 as residues: Glu-50 to Glu-61.

The tissue distribution in human striatum depression suggests that the protein product of this clone would be useful for study and treatment of central nervous system disorders, such as seizures and other neurological conditions. The protein product  
20 of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal  
25 cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role  
30 in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal

differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
10 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 294 of SEQ ID NO:71, b is an integer of 15 to 308, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 62**

This clone has homology to a cystine rich granulin peptide(s) from leucocyte(s) which has been termed Granulin E. Granulins inhibit keratinocytes and is useful topically for wound healing. The gene encoding the disclosed cDNA is  
20 believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

It has been discovered that this gene is expressed primarily in infant brain.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
25 diagnosis of the following diseases and conditions: neurological, developmental, and growth defects. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetus and the nervous system, expression of this gene at  
30 significantly higher or lower levels may be detected in certain tissues (e.g., neural, developmental, growth, and cancerous and wounded tissues) or bodily fluids (e.g.,

lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Based on the strong conservation of cysteine residues, the polypeptide of the present invention can be used to inhibit keratinocytes and promote wound healing.

The tissue distribution in infant brain suggests that the protein product of this clone would be useful for study and treatment of nervous system, neurodegenerative and developmental disorders. The protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The homology to granulin proteins suggest the protein product of this clone is useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus),

keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athletes foot, and ringworm). Moreover, the protein product of this clone may also be useful for the treatment or diagnosis of various connective tissue disorders such as arthritis, trauma, tendonitis, chondromalacia and inflammation, autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1674 of SEQ ID NO:72, b is an integer of 15 to 1688, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 63**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: SNAAGNVVRAFLYINHLKL GCKVGLA (SEQ ID NO:276). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in prostate cancer and dendritic cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: reproductive, immune, and hematopoietic diseases, defects and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 170 as residues: Trp-47 to Thr-54.

The tissue distribution in prostate cells and tissues indicates that the protein products of this clone are useful for study, diagnosis and treatment of neoplasias, esp. of the prostate, and hormonal and metabolic disorders. Moreover, the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1124 of SEQ ID NO:73, b is an integer of 15 to 1138, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 64**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: NWAVLNMLLSKKGKITIFLGPLECGS (SEQ ID NO:277). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in B cell lymphoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and hematopoietic diseases, disorders, and/or defects, particularly cancers. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hemopoietic and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.



The tissue distribution in B cell lymphoma suggests that the protein product of this clone would be useful for study and treatment of blood and immune disorders and neoplasias, esp. of the lymphatic system. The protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 763 of SEQ ID NO:74, b is an integer of 15 to 777, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 65**

It has been discovered that this gene is expressed primarily in B cell lymphoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune and hematopoietic diseases, disorders, and/or defects, particularly cancer. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hemopoietic and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in B cell lymphoma suggests that the protein product of this clone would be useful for study and treatment of neplasias, esp. of lymphatic organs, and immune disorders. The protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
 5 general formula of a-b, where a is any integer between 1 to 1046 of SEQ ID NO:75, b is an integer of 15 to 1060, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

#### 10. FEATURES OF PROTEIN ENCODED BY GENE NO: 66

The translation product of this gene shares sequence homology with a rat protein phosphatase, in addition to, a human heterogeneous nuclear ribonucleoprotein R (See Genbank Accession No.gil2697103 (AF000364)). When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1  
 15 (early growth response gene 1) promoter element. Thus, it is likely that this gene activates sensory neuron cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. This gene also showed activity in  
 20 sensory neurons using the EGR assay described in the Example section.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PSHQTRKGKSAKLLDRPPEALRMKIITTTLLACHLQLEV  
 G V V V G G E V D ( S E Q I D N O:278),  
 FQASSANNQQNWGSQPIAQQPLQQGGDYSG  
 25 NYGYNNDNQEFYQDTYGQQWK (SEQ ID NO:279), WXPLLXTSGSPGLXGFG  
 TRMNGKEIEGEEIEIVLAKPPDKKRKERQAARQASRSTAYEDYYYHPPPRMPP  
 PIRGRGRGGGRGGYGYPDYGYEDYYDDYYGYDYHDYRGGYEDPYYGYD  
 DGYAVRGRGGGRGGRGAPPPRGRGAPPPRGRAGYSQRGAPLGPPRGSRRG  
 RGGPAQQQRGRGSRGSRGNRGGNVGGKRKADGYNQPSKRRQPTTNRGTG  
 30 PNPSLSSRFSKVVTILVTMVTIMTTRNFIRILMGNSGSRQVRA (SEQ ID  
 NO:280), RMNGKEIEGEEIEIVLAKPPDKKRKER (SEQ ID NO:281), YYHPPP

RMPP PIRGRGRGGGRGGYG (SEQ ID NO:282), DYRGGYEDPYGYDDGYAV  
RGRGGGR (SEQ ID NO:283), PPRGRAGYSQRGAPLGPPRGSRGGRGG (SEQ  
ID NO:284), and/or ADGYNQPDSK RRQPTTNRTGVPNPSLSSRFSKVVT (SEQ  
ID NO:285). Polynucleotides encoding these polypeptides are also encompassed by  
5 the invention. The gene encoding the disclosed cDNA is believed to reside on  
chromosome 1. Accordingly, polynucleotides related to this invention are useful as  
a marker in linkage analysis for chromosome 1.

It has been discovered that this gene is expressed primarily in human primary  
breast cancer, lung, and leukocytes.

10 Therefore, nucleic acids of the invention are useful as reagents for differential  
identification of the tissue(s) or cell type(s) present in a biological sample and for  
diagnosis of the following diseases and conditions: reproductive, immune, or  
pulmonary diseases and/or disorders, particularly breast cancer. Similarly,  
polypeptides and antibodies directed to those polypeptides are useful to provide  
15 immunological probes for differential identification of the tissue(s) or cell type(s). For  
a number of disorders of the above tissues or cells, particularly of the reproductive,  
immune and respiratory systems, expression of this gene at significantly higher or  
lower levels may be detected in certain tissues or cell types (e.g., reproductive,  
immune, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g.,  
20 lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual  
having such a disorder, relative to the standard gene expression level, i.e., the  
expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in breast cancer cells and tissues, in addition to immune  
cells, combined with the homology to a protein phosphatase suggests that the protein  
25 product of this clone would be useful for diagnosis and treatment of breast cancer and  
abnormalities of the lung and the immune system. Moreover, the expression of this  
gene product suggests a role in regulating the proliferation; survival; differentiation;  
and/or activation of hematopoietic cell lineages, including blood stem cells. This gene  
product may be involved in the regulation of cytokine production, antigen  
30 presentation, or other processes suggesting a usefulness in the treatment of cancer  
(e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues.

Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein is useful in modulating the immune response to aberrant cells and cell types, particularly proliferative cells (e.g. protein may increase the immunogenicity of tumor antigens either directly or indirectly, or may activate apoptosis). The protein is useful in treating, detecting, and/or preventing various pulmonary disorders, which include, but are not limited to, ARDS, emphysema, and cystic fibrosis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1489 of SEQ ID NO:76, b is an integer of 15 to 1503, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 67

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: LQIPPSSQSLGLKNADSSI (SEQ ID NO:286), GGPPESAPW LPAVLRAPVLT SRCASSDSEGPVWFCQPGSGPSSTEMSCHCILGPGSSCLCVL RGSMTWTPSVPGWPQPAKETGASSCSVFSANNGSCPLPLHNHQRQASLDTGL SLEHVPGESYFYSPVG (SEQ ID NO:287), SSDSEGPVWFCQPGSGPSSTEMSC  
10 HCILGPGSSC (SEQ ID NO:288), WTPSVPGWPQPAKETGASSCSVFSANNG (SEQ ID NO:289), and/or QRQASLDTGL SLEHVPGESYF (SEQ ID NO:290).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in human B cell lymphoma.

15 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune or hematopoietic diseases and/or disorders, particularly B cell lymphoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes  
20 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an  
25 individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in B-cell lymphoma suggests that the protein product of this clone would be useful for diagnosis and treatment of immune or hematopoietic diseases and/or disorders, particularly proliferative conditions. Moreover, the  
30 expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including

blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene  
5 product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to  
10 transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other  
15 blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of  
20 neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as,  
25 antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of  
30 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence

would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 858 of SEQ ID NO:77, b is an integer of 15 to 872, where both a and b correspond to the positions of  
5 nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 68**

In specific embodiments, polypeptides of the invention comprise the following  
10 amino acid sequence: SSSLVLTIRSQTLFLASFIHSTSIFCALN (SEQ ID NO:291). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in osteoarthritic cartilage.

Therefore, nucleic acids of the invention are useful as reagents for differential  
15 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: osteoarthritis and other bone/cartilage disorders, particularly degenerative conditions. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of these tissue(s) or cell type(s). For a number of  
20 disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., skeletal, joint, autoimmune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression  
25 level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in osteoarthritic cartilage suggests that the protein product of this clone would be useful for the diagnosis, treatment, and/or prevention of osteoarthritis. Moreover, the gene product is useful in the detection and treatment  
30 of disorders and conditions affecting the skeletal system, in particular osteoporosis, bone cancer, as well as, disorders afflicting connective tissues (e.g. arthritis, trauma,



tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 559 of SEQ ID NO:78, b is an integer of 15 to 573, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 69**

The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

It has been discovered that this gene is expressed primarily in fetal brain, pharynx carcinoma, and Hodgkin's lymphoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: developmental and/or proliferative diseases and disorders, particularly pharynx carcinoma, and Hodgkin's lymphoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to

provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, proliferative cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 176 as residues: Tyr-30 to Ser-40.

The tissue distribution in pharynx carcinoma and Hodgkin's lymphoma suggests that the protein product of this clone would be useful for diagnosis and treatment of immune and proliferative conditions. Moreover, expression within fetal tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.

Alternatively, the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia,

trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep  
5 patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein  
10 may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of  
15 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1495 of SEQ ID NO:79, b  
20 is an integer of 15 to 1509, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 70**

25 The translation product of this gene shares sequence homology with insulin-like growth factor binding protein. Moreover, the protein has homology to the human Slit-1 protein (See Genbank Accession No. gnlIPID1036170 (AB017167)), which is thought to play an integral role in neural development. In Drosophila embryogenesis, the slit gene has been shown to play a critical role in CNS midline formation. Each  
30 Slit gene encodes a putative secreted protein, which contains conserved protein-protein interaction domains including leucine-rich repeats (LRR) and epidermal

growth factor (EGF)-like motifs, like that of the *Drosophila* protein. The Slit genes form an evolutionary conserved group in vertebrates and invertebrates, and the mammalian Slit proteins may participate in the formation and maintenance of the nervous and endocrine systems by protein-protein interactions.

- 5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: the EGF-like domain: CCCRLGLSGPKC (SEQ ID NO:292); in addition to the following: RAFWGLGALQLLDLSANQLEAL (SEQ ID NO:293), HASGRRTGSADDGLQGRTGSGPPTAGAGGGGAAP (SEQ ID NO:294), VSAAAGARLAPRAPGAPAGCRPMRGCAARAAARKSLVPVLPAGWRS GPAA
- 10 AARPGPRRLAHAPSAARSRAGPGAVARPLPRRH LAAAHGRGCGPAAARAGA GSGPGARRAARVPTAGRPPGTHVHTSGQSGAPRDPEGEALADTWAQTGQGD SSSNSSSSGRGRDQEGPRMGAAPPPAPAVGGPLPVRPWSPSSAEPVLRPDAW ( S E Q I D N O : 2 9 5 ) , TRPAAERAPRTTGSRDAQAAGLPPRVPGAGGLPPCGALPGR
- 15 GLGRCCCCCCCCRLGLSGPKCRPGPRPRGPWAPRTAPRCARACREACQLSAL SLPAVPPGLSLRLRALLLDHNRVRALPPGAFAGAGALQRLDLRENGLHSVHV RAFWGLGALQLLDLSANQLEALAPGTFAPLRALRNLSLAGNRLARLEPAALG ALPLLRSLSLQDNELAALAPGLLGRLPALDALHLRGNPWGCGCALRPLCAWL RRHPLPASEAETVLCVWPGRLTLSPLTAFSDAAFSHCAQPLALRDLARGLHA
- 20 RAGLLPRQPGLPGAGLWAHRLPCAPPPPHRRPPPAETVQTRTPIPTPTAVPR P R T R G A P S A A A Q A ( S E Q I D N O : 2 9 6 ) , GCRPMRGCAARAAARKSLVPVLPAGWRS GP AAAARPGPRRLAHAPSA (SEQ ID NO:297), PGAVARPLPRRH LAAAHGRGCG PAAARAGA (SEQ ID NO:298), SGQSGAPRDPEGEALADTWAQTGQ (SEQ ID NO:299),
- 25 PPAPAVGGPLPVRPWSPSSAEPV (SEQ ID NO:300), APRTTGSRD AQAAGLPPRVPGAGGLP (SEQ ID NO:301), GPRPRGPWAPRTAPRCARACRE (SEQ ID NO:302), AVPPGLSLRLRALLLDHNRVRALPPGAFAGA (SEQ ID NO:303), LGALQLLDLSANQLEALAPGTFAP (SEQ ID NO:304), PPGAFAGAG ALQRLDLRENGLHSVHVRAFWGLGALQ (SEQ ID NO:305), RNLSLAGNRLA
- 30 RLEPAALGALPLLRSL (SEQ ID NO:306), LPALDALHLRGNPWGCGCALRP LCAW (SEQ ID NO:307), TVLCVWPGRLTLSPLTAFSDAAFSHCAQPLALRD

(SEQ ID NO:308), LHARAGLLPRQPGFLPGAGLWAHR (SEQ ID NO:309), and/or TVQTRTPIPTPTAVPRPRTRGAPS (SEQ ID NO:310). Polynucleotides encoding these polypeptides are also encompassed by the invention.

5 It has been discovered that this gene is expressed primarily in a breast cancer cell line, MDA36.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neural, reproductive, and proliferative diseases and/or disorders, particularly breast cancer and degenerative  
10 conditions. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, reproductive, and  
15 proliferative cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
20 177 as residues: Met-1 to Arg-10, Arg-64 to Ala-71, Gly-124 to Gly-131, Pro-189 to Arg-194, Val-223 to Gly-228.

The tissue distribution in a breast cancer cells and tissues and homology to insulin-like growth factor binding protien suggests that the protein product of this clone would be useful for diagnosis and treatment of breast cancer, and other forms of  
25 cancer. Moreover, the homology to the conserved human slit-1 protein suggests that the protein is useful in the treatment, diagnosis, and/or prevention of neural disorders, particularly developmental and degenerative conditions. Similarly, the protein is useful for the treatment and/or diagnosis of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to  
30 Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia,

trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1095 of SEQ ID NO:80, b is an integer of 15 to 1109, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 71**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HASGRPDRSSAPIGNSGLPCPDLEPLGGLQSKCRLCAPTEARGLWSRSLCSDRCTWRS (SEQ ID NO:311), and/or GLPCPDLEPLGGLQSKCRLCAPTEARGLW (SEQ ID NO:312). Polynucleotides encoding these polypeptides are also encompassed by the invention. This gene also maps to chromosome 1, and therefore can be used in linkage analysis as a marker for chromosome 1.

It has been discovered that this gene is expressed primarily in salivary gland and colon carcinoma.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: colon carcinoma and other digestive system or gastrointestinal diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression  
10 of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., digestive system, gastrointestinal, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, chyme, bile, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy  
15 tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 178 as residues: Val-34 to Leu-39, Ser-64 to Cys-74, Ser-86 to Ser-95, Arg-128 to Ala-136.

The tissue distribution in salivary gland and colon carcinoma suggests that the  
20 protein product of this clone would be useful for the treatment and diagnosis colon cancer and other digestive system diseases and/or disorders, such as ulcers, and other proliferative conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence  
30 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 793 of SEQ ID NO:81, b is an integer of 15 to 807, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

5

## FEATURES OF PROTEIN ENCODED BY GENE NO: 72

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: QEWESELGERRKPLQA (SEQ ID NO:313). Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 It has been discovered that this gene is expressed primarily in 6 week old human embryos.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: embryological defects; aberrant development; aberrant cellular proliferation (e.g. cancers), and other developmentally related or proliferative diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing human embryo, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

25

The tissue distribution in 6 week old human embryos suggests that the protein product of this clone would be useful for the diagnosis and/or treatment of defects in embryonic development. Elevated expression of this gene product in early 6 week human embryos suggests that this gene product plays a critical role in normal human development. Alternatively, this gene product may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant

30



Expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Moreover, this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1029 of SEQ ID NO:82, b is an integer of 15 to 1043, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 73

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: CQSSNLIFFQFVNILFNLMMMDILVDFSITKMPINSIFSLYF

CYEII (SEQ ID NO:314). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in 6 week old human embryo.

5           Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: abnormal embryonic development; abnormal cellular proliferation; developmental defects, and other developmentally related or proliferative diseases and/or conditions. Similarly,  
10 polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing human embryo, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, and cancerous and  
15 wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in 6 week old human embryo suggests that the protein  
20 product of this clone would be useful for the diagnosis and treatment of disorders of human embryonic development. Expression of this clone in developing embryos suggests that it plays a critical role in early human development. Alternatively, it may be involved in key cellular proliferation events that occur during embryogenesis. Therefore misexpression of this gene in adult tissues may lead to abnormal patterns of  
25 cellular proliferation and cancer. Moreover, expression within embryonic tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.  
30 Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell

death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1159 of SEQ ID NO:83, b is an integer of 15 to 1173, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 74

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: GPVWLFCLTLCKPSQLFSQENSCMDVAGGVTTCLPP WFSRGAPAQMSQWPPSSDHGAVRAGRDSRVGPVQPSHLTCEGGKEEREKNK KAEVNPPTGMGLANRIPRDDITLKLNRNQGKLRTKENRTQSAKRHP (SEQ ID NO:315), VACKPENRTKTHFASSPACDGHALGGQVGFAICFLSCLFPPM (SEQ ID NO:316), and/or SHPMPNTPQKQLLFSEDNELLVSLRTGRKPTLQAALRVTG (SEQ ID NO:317). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in pleural cancer and endometrial tumors, and, to a lesser extent, in bone marrow & apoptotic T cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: pleural cancer; endometrial tumors; hematopoietic disorders; immune dysfunction. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lungs and immune system, expression  
10 of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not  
15 having the disorder.

The tissue distribution in pleural cancer and endometrial tumors indicates that the protein products of this clone are useful for the diagnosis and treatment of various reproductive cancers, including pleural cancer and endometrial tumors. In addition,

Expression of this gene product within T cells & bone marrow suggests that it  
20 may play a role in normal hematopoiesis. Therefore, this gene product may also be useful in the diagnosis and/or treatment of a variety of hematopoietic disorders, including defects in immune surveillance, inflammation, impaired immune function, and T cell lymphomas. Use of this gene product may be appropriate in situations designed to affect the proliferation, survival, and/or differentiation of various  
25 hematopoietic cell lineages, including blood stem cells.

Moreover, this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can  
30 result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in

acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein  
 5 may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
 10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
 15 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1547 of SEQ ID NO:84, b is an integer of 15 to 1561, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.

20

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 75

The translation product of this gene shares low sequence homology with dreg-2, a gene product originally identified in *Drosophila* that shows an oscillating pattern of expression tied into a circadian clock rhythm.

25 In specific embodiments, polypeptides of the invention comprise the following  
 a m i n o a c i d s e q u e n c e :  
 AHRLQIRLLTWDVKDTLLRLRHPLGEAYATKARAHGLEV  
 EPSALEQGGFRQAYRAQSHSFPNYGLSHGLTSRQWWLDVVLQTFHLAGVQDA  
 QAVAPIAEQLYKDFSHPCWTQVLDGAEDTLRECRTRGLRLAVISNFDRRLEGI  
 30 LXGLGLREHFDFVLTSEAAGWPKPDPRIFQEALRLAHMEPVVAAHVGDNLYL  
 CDYQGPRAVGMHSFLVVGPPALDPVVRDSVPKEHILPSLAHLLPALDCLEGS

T P G L ( S E Q I D N O:319),  
 EGDPRGRPRRPLGPPPQLTLPTALXDILRQVRAPGLRLSRA  
 LEVGRKGSPIFKIQIYL (SEQ ID NO:318), IRLLTWDVKDTLLRLRHPLGEAYA  
 TKA (SEQ ID NO:320), LEQGFRQAYRAQSHSFPNYGLSHG (SEQ ID NO:321),  
 5 HLAGVQDAQAVAPIAEQLYKDFSHPC (SEQ ID NO:322), VLDGAEDTLRECR  
 TRGLRLAVIS (SEQ ID NO:323), REHFDFVLTSEAAGWPKPDPRIFQEA (SEQ  
 ID NO:324), EPVVAAHVGDNYLCDYQGPRAVGMHSFL (SEQ ID NO:325),  
 and/or VVRDSVPKEHILPSLAHLLPALD (SEQ ID NO:326). Polynucleotides  
 encoding these polypeptides are also encompassed by the invention.

10 It has been discovered that this gene is expressed primarily in tumors of the  
 pancreas & thymus and to a lesser extent in a variety of fetal tissues, including fetal  
 brain, liver, spleen, and kidney.

Therefore, nucleic acids of the invention are useful as reagents for differential  
 identification of the tissue(s) or cell type(s) present in a biological sample and for  
 15 diagnosis of the following diseases and conditions: pancreatic cancer; thymic cancer;  
 disorders of fetal development; abnormal cellular proliferation; hematopoietic  
 disorders. Similarly, polypeptides and antibodies directed to those polypeptides are  
 useful to provide immunological probes for differential identification of the tissue(s)  
 or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
 20 the pancreas and immune system, expression of this gene at significantly higher or  
 lower levels may be detected in certain tissues or cell types (e.g., developmental,  
 metabolic, immune, hematopoietic, and cancerous and wounded tissues) or bodily  
 fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid or spinal fluid)  
 taken from an individual having such a disorder, relative to the standard gene  
 25 expression level, i.e., the expression level in healthy tissue from an individual not  
 having the disorder.

The tissue distribution in proliferative and developmental cells and tissues  
 indicates that the protein products of this clone are useful for the diagnosis and  
 treatment of cancers, particularly pancreatic and thymic cancer. Expression of this  
 30 gene product within various fetal tissues also indicates that it is useful in the diagnosis  
 and/or treatment of human developmental disorders. Taken together, the observation

that this gene product is expressed in cancers and in fetal tissues indicates that it plays a role in proliferation and/or differentiation events that are associated with early development. Misexpression of this gene product in adult tissues, therefore, may directly contribute to abnormal cellular proliferation and/or dedifferentiation that  
5 accompanies cancer. Finally,

Moreover, the expression of this gene product in fetal liver/spleen also suggests that it plays a role in hematopoiesis, and is useful in the diagnosis and/or treatment of a variety of disorders of the immune system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or  
10 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically  
15 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1419 of SEQ ID NO:85, b is an integer of 15 to 1433, where both a and b correspond to the positions of  
20 nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 76**

In specific embodiments, polypeptides of the invention comprise the following  
25 amino acid sequence: IRKLGPGGLAPCSCRSGQVFPRV (SEQ ID NO:327).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in frontal cortex, particularly derived from epileptic patients.

Therefore, nucleic acids of the invention are useful as reagents for differential  
30 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: epilepsy; neurodegenerative

diseases and disorders, particularly learning disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, CNS, and/or PNS, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in frontal cortex tissue suggests that the protein product of this clone would be useful for the diagnosis and/or treatment of disorders of the brain and nervous system, particularly epilepsy. Moreover, the expression of this gene product suggests that it may play a role in various critical processes of the nervous system, including nerve survival, pathfinding, signal conductance, and/or synapse formation. It may have effects on various processes including homeostasis, learning, motor function, language, etc. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1363 of SEQ ID NO:86, b is an integer of 15 to 1377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.



**FEATURES OF PROTEIN ENCODED BY GENE NO: 77**

In specific embodiments, polypeptides of the invention comprise the following

a m i n o                                      a c i d                                      s e q u e n c e :

- 5 KPLRMARPGGPEHNEYALVSAWHSSGSYLDSEGLRHQDD  
FDVSLLVCHCAAPFEEQGEAERHVLRLQFFVVLTSQRELFPRLTADMRRFRK  
PPRLPPEPEAPGSSAGSPGEASGLILAPGPAPLPPLAAEVGMARARLAQLVRL  
AGGHCRDRTLWKRLFLLEPPGPDRRLRLGGRLALAELEELLEAVHAKSIGDIDP  
QLDCFLSMTVSWYQSLIKVLLSRFPRAVAISKAQTWELSTWLR (SEQ ID  
10 NO:328), ARGTLELPTPLIAAHQLYNYVADHASSYHM (SEQ ID NO:329),  
SHCEWPGQG AQNTTSMPWCRHGTVLAPTWTLRDFDTR (SEQ ID NO:330),  
PLTTVSHLCPL  
SLRVFTSHLDITAGHSHRDDTWVPIPALPLKHLRPPSSPFALGPWVSHPLMRW  
VQKLSHLHSNPGTGFSMGGKSAEKLKC (SEQ ID NO:331), STAARGAPGPGR  
15 AGGTPRSSPCQIHWGHRPPAGLLPIHDGLLVPEPDQSSPKPLPQSCRHFQSPDL  
GTQYLVALNQKFTDCSALVFWTPLRKDVSEVVFREALPVQPQDTRSPPAQLV  
STYHHLESVINTACFTLLDPPPLKGVDTTECHCSLNHGPTRLPARGRTDQPF  
W A P G Q A R H                      ( S E Q                      I D                      N O : 3 3 2 ) ,  
HQRLCNYVLRVCCPSLAAGTALPKHPQPLTHPGL  
20 QRV RSTPRTPWALLGY SFRPPW                      (SEQ ID NO:333),  
PGGPEHNEYALVSAWHSS GSYLDSEGLR (SEQ ID NO:334),  
DVSLLVCHCAAPFEEQGEAERHVLRL (SEQ ID NO:335),  
RLTADMRRFRKPPRLPPEPEAPGSSAGS (SEQ ID NO:336), GEASGLI  
LAPGPAPLPPLAAEVGM                      (SEQ ID NO:337),  
25 TLWKRLFLLEPPGPDRRLRLGGRL (SEQ ID NO:338), and/or  
LAELEELLEAVHAKSIGDIDPQLDCFLS (SEQ ID NO:339). Polynucleotides  
encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in fetal liver/spleen and leukocytes, and to a lesser extent in a colon adenocarcinoma cell line.

- 30 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for

diagnosis of the following diseases and conditions: hematopoietic disorders; immune dysfunction; colon cancer; colorectal adenocarcinoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
5 of the above tissues or cells, particularly of the immune system and colon, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., hematopoietic, immune, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard  
10 gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 184 as residues: Leu-16 to Ser-23, Ser-38 to Pro-43, Gly-53 to Leu-60.

The tissue distribution in colon adenocarcinoma suggests that the protein  
15 product of this clone would be useful for the diagnosis and/or treatment of gastrointestinal diseases and/or disorders, particularly proliferative conditions. Expression of this gene product in fetal and proliferative cells and tissues suggests that it may be a marker cancers, and that its misregulated expression may in fact contribute to the development or progression of the types of cancers dictated by its  
20 expression.

Similarly, the expression of this gene product in fetal liver/spleen - a primary site of early hematopoiesis - taken together with its expression in peripheral blood leukocytes suggests that this gene product may play a role in a variety of hematopoietic processes, including the survival, proliferation, activation, and/or  
25 differentiation of all blood cell lineages, including the totipotent hematopoietic stem cell. Such a gene product may therefore play a role in a variety of hematopoietic disorders including inflammation; immune dysfunction; defects in immune surveillance; and hematopoietic cancers and lymphomas. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern  
30 formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent

of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1701 of SEQ ID NO:87, b is an integer of 15 to 1715, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 78**

The gene encoding the disclosed cDNA is believed to reside on chromosome 20. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 20.

It has been discovered that this gene is expressed primarily in brain.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neurodegenerative diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s)

or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. This gene is believed to reside on chromosome 20, D20S111-D20S195. Polynucleotides corresponding to this gene are useful, therefore, as chromosome markers.

10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 185 as residues: Met-1 to Tyr-6, Thr-38 to Ala-44.

The tissue distribution in brain tissue indicates that the protein products of this clone are useful for diagnosis and treatment of disorders of the central nervous system. Moreover, the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

25 In addition, elevated expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 403 of SEQ ID NO:88, b is an integer of 15 to 417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

10

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 79

When tested against U937 cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, other immune and hematopoietic cells or cell types, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: FQLYFNPELIFKHFQIWRLITNFFGPGVGFNFLNMFILYRYCRMLEEGSFRGRTADFVFMFLFGGFLMTLFGFLVSLVFLGQAFTIMLVYVWSRXNPYVRMNFGLLNQAPFLPWVLMGFSLLLGNSIIVDLLGIAVGHIYFFLEDVFPNQPGGIRILKTPSILKAIFDTPDEDPNYNPLPEERPGGFAWGEGQ SEQ ID NO: 340), GVGQATVGKMAYQSLRLEYLQIPPVSRAYTTACVLTTAAVQLELITPFLYFNPELIFKHFQIWRLITNFFGPGVGFNFLNMFILYRYCRMLEEGSFRGRTADFVF (SEQ ID NO:341), LIFKHFQIWRLITNFFGPGVGF (SEQ ID NO:342), FLYRYCRMLEEGSFRGRTADFVFMF (SEQ ID NO:343), LVFLGQAFTIMLVYV

30

WSRXNPYV (SEQ ID NO:344), VLMGFSLLLGNSIIVDLLGIA (SEQ ID NO:345), NQPGGIRILKTPSILKAIFDTPDED (SEQ ID NO:346), RLEYLQIPPVSRAYTTAC VLTAAVQLE (SEQ ID NO:347), and/or RLITNFLFFGPVGFNLFNMIFLYRYC RMLE (SEQ ID NO:348). Polynucleotides encoding these polypeptides are also  
5 encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 17.

It has been discovered that this gene is expressed primarily in smooth muscle, fetal brain, fetal liver and to a lesser extent in activated macrophage, colon cancer.

10 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: developmental diseases, immune-related diseases, neural disorders, and vascular diseases and conditions. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide  
15 immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, vascular, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,  
20 plasma, amniotic fluid, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in fetal liver, macrophage, and fetal brain indicates that the protein products of this clone are useful for treating and diagnosis of immune  
25 system-related diseases and CNS diseases. Moreover, the protein product of this clone is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex- vivo culture, bone marrow transplantation, bone marrow  
30 reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as

infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the protein is useful in the detection, treatment, and/or prevention of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or embolism.

Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells, combined with the GAS biological activity, suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention

are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1153 of SEQ ID NO:89, b is an integer of 15 to 1167, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 80

The translation product of this gene shares sequence homology with proacrosin binding proteins (sp32) from non-human mammalian species. The binding of sp32 to proacrosin may be involved in packaging the acrosin zymogen into the acrosomal matrix. See, for example, J Biol Chem. 1994 Apr 1; 269(13): 10133-10140, incorporated herein by reference. Accordingly, the inventors have termed the translation product of this gene human sp32 or "h-sp32". Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of PMN to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both neutrophils, and to a lesser extent in other immune and hematopoietic cells. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HASAGPDGSSPA (SEQ ID NO:349), ELLLEKPKPWQPPAAAPHRALLVLCYSIVENTCIITPTAKAWKYMEEEILGFG KSVCDLGRHRMSTCALCDFCSLKLEQCHSEASLQRQQCDTSHKTPFAAPCL P P R A C P S A T R ( S E Q I D N O : 3 5 0 ) , LPGWGFPTKICDTDYIQYPNYCSFKSQCLMR NNRNKVSRMRCLQNETYSALSPGKSEDVVLRWSEQFSTLTGQFG (SEQ ID NO:351), SPVLLPAFPPLPVPLLALPVSAPLPACVLVSAPACAPLLAPACAL ALAPGFPGTRRIVGALPRCC (SEQ ID NO:352), LLVLCYSIVENTCIITPTAK AWKYMEEEILGFGKS (SEQ ID NO:353), and/or LKLEQCHSEASLQRQQC DTSHKTPFA (SEQ ID NO:354). Polynucleotides encoding these polypeptides are



also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 12. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 12.

It has been discovered that this gene is expressed primarily in testis.

5 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: reproductive disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For  
10 a number of disorders of the above tissues or cells, particularly of the reproductive diseases, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, testis, prostate, epididymus, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having  
15 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. This gene is believed to map to chromosome 12 and is thought to be useful as a chromosome marker.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
20 187 as residues: Asp-27 to Ser-32, Pro-52 to Thr-58, Arg-63 to Asn-70, Gln-78 to Gly-83, Thr-107 to Asn-113, Thr-160 to Val-176, Ser-188 to Gly-241, Leu-248 to Pro-265, Tyr-302 to Gly-314.

The tissue distribution in testis, combined with the specific homology to the sp32 protein indicates that the protein products of this clone are useful for the  
25 diagnosis, treating, and/or prevention of reproductive diseases and/or disorders. Moreover, polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is  
30 also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents.

Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. The protein is useful in application and utility as a contraceptive, either directly or indirectly. Based upon the detected calcium flux activity, the protein may also be useful as an effect treatment for infertility (i.e. for inhibiting autoimmune disorders). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1878 of SEQ ID NO:90, b is an integer of 15 to 1892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

#### FEATURES OF PROTEIN ENCODED BY GENE NO: 81

The translation product of this contig has consistent sequence homology with a number of previously described viral tat proteins (see, for example, Stevens, et al., J. Virol. 64:3716-3725 (1990), which is hereby incorporated by reference, herein).

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: QVSGILSLSCGMDGLALDGSPSPSPXTEKAGRCISQTSL (SEQ ID NO:355), QVSGILSLSCGMDGLALDGSPSPSPXTEKAGRCISQTSLP GKWEV (SEQ ID NO:356), RASKTVPRMPPNWPAPKMPCLCHIRTV EHLGTIS

SGAPGRPTGQQAARTYHICWIHPGQKIDSLPPSSQHPRSQQ LAPGTWPSTSTT  
 KPAEETLGSSASLPISQARKSEKCTFQPSWPXVRGKESHQVPAHPSHRTETES  
 D HSPVRKPPSRGTRTGDFTVGDWSEAWLLELALL (SEQ ID NO:357), RMPPN  
 WPAKMPCLCHIRTVEHLG (SEQ ID NO:358), GRPTGQQAARTYHICWIHPG  
 5 QKIDS (SEQ ID NO:359), WPSTSTTKPAEETLGSSASLPISQA (SEQ ID NO:360),  
 KSEKCTFQPSWPXVRGKESHQVP (SEQ ID NO:361), and/or KPPSRGTRTGDFTVGDWSEAWLLE (SEQ ID NO:362). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed almost exclusively in  
 10 neutrophils.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential  
 15 identification of the tissue(s) or cell type(s). For a number of disorders of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard  
 20 gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. In addition, molecules of the present invention can be used to regulate transcription and translation of genes in cells of the immune system, as well as in other cell types. Such transcriptional and translation regulation is useful for diagnosing and treating a number of disorders in which an altered state of  
 25 transcription and translation may be a factor in the disorder. Such disorders include many viral infections, particularly of immune cells, including HIV-1, HIV-2, human T-cell lymphotropic virus (HTLV)-I, and HTLV-II, as well as other DNA and RNA viruses such as herpes simplex virus (HSV)-1, HSV-2, HSV-6, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes samirii, adenoviruses, rhinoviruses,  
 30 influenza viruses, reoviruses, and the like. In addition, the ability to use molecules of the present invention to molecularly regulate the processes of transcription and

translation is useful in the diagnosis and treatment of many types of cancers, particularly those of the immune system, including ovarian cancer, breast cancer, colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, and the like.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 188 as residues: Gln-2 to Trp-12, Ala-30 to Glu-35, Gln-42 to Ser-51.

The tissue distribution in neutrophils, combined with the homology to viral tat proteins suggests that the protein product of this clone is useful for the diagnosis and treatment of immune disorders, particularly viral infections and proliferative disorders. Further, since this clone has a high degree of sequence relatedness to factors which are involved in the regulation of transcription and translation, this clone is useful as a regulator of such processes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 509 of SEQ ID NO:91, b is an integer of 15 to 523, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 82**

The translation product of this contig has clear sequence identity with a number of thioredoxins and endoplasmic reticulum resident proteins (see, for

example, Shorrosh and Dixon, Plant J. 2:51-58 (1992), which is hereby incorporated by reference, herein).

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PCADCLSAWA (SEQ ID NO:363). Polynucleotides encoding  
5 these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

It has been discovered that this gene is expressed primarily in adipocytes and  
10 striatum depression, and in lower abundance in prostate, whole brain, fetal liver, and spleen.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: Prostate cancer, CNS diseases,  
15 immune disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, hematopoietic,  
20 immune, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Since the translation product of this clone has a high degree of sequence relatedness  
25 to many thioredoxins, it can be used as a food additive to improve flour quality or to suppress the anti-nutritional effects of leguminous plants. Molecules of the present invention can further used to inactivate toxins, for example, bee or snake venom.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 189 as residues: Trp-43 to Ala-49, Pro-68 to Ala-74, Glu-100 to Gly-111, Glu-120 to  
30 Asn-125, Pro-141 to Ala-154, Asp-157 to Lys-171, Cys-177 to Ile-182, Ser-248 to Leu-253, Thr-280 to Glu-285, Gly-353 to Val-359.

The tissue distribution in whole brain suggests that the protein product of this clone would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, 5 Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including 10 disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The secreted protein can also be used to determine 15 biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating 20 human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); 25 hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies 30 directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1368 of SEQ ID NO:92, b is an integer of 15 to 1382, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 83**

When tested against TF-1 cell lines, supernatants removed from cells containing this gene activated the ISRE (interferon-sensitive responsive element ) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, in immune and hematopoietic cells or tissues, through the JAK-STAT signal transduction pathway. ISRE is a promoter element found upstream in many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: HASGYLCIVLL (SEQ ID NO:364). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed exclusively in Rejected Kidney.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: kidney and other urinary tract

disorders and disorders related to, or resulting from, transplantation. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and renal systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., renal, kidney, urogenital, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Molecules of the present invention are particularly useful in the diagnosis and treatment of disorders related to transplantation, particularly kidney transplantation.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 190 as residues: Asn-49 to Gln-54, Glu-150 to Asp-159.

The tissue distribution in rejected kidney tissue suggests that the protein product of this clone would be useful for diagnosis and treatment of disorders related to or resulting from rejection of transplanted organs, particularly the kidney. Moreover, the protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Considering the tissue distribution and detected ISRE biological activity, the protein is useful in modulating the immune response to aberrant kidney proteins, including autoantigens and aberrant proteins which are often present in degenerative and proliferative conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly available prior to conception of



the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
5 general formula of a-b, where a is any integer between 1 to 1733 of SEQ ID NO:93, b is an integer of 15 to 1747, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

#### 10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 84**

The translation product of this gene shares sequence homology with the conserved MAL and plasmolipin protein (Magyar, et al, Gene 189:269-275 (1997); See Genbank Accession No.gnllPIDle183885), which are thought to be important in modulating T cell function, and proper CNS function, respectively. When tested  
15 against Jurkat cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent, immune or hematopoietic cells and tissues, through the JAK-STAT signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT  
20 pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise the following  
25 amino acid sequence: NSARAARAEIVLGLLVWTLIAGTEYFRVPAFGWV (SEQ ID NO:365). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in T cells.

Therefore, nucleic acids of the invention are useful as reagents for differential  
30 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of immune, hematopoietic, and neural diseases and/or disorders. Similarly,

polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in

5 certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Nucleic acids of the present invention are useful as probes for

10 detecting traumatic and pathological changes in the central and peripheral nervous systems. Molecules of the present invention may be involved in regulating the growth of Schwann cells and other neural cells. Molecules of the present invention are also useful as modulators of the interaction between Schwann cells and other neural cells and the extracellular matrix and is therefore useful for the therapeutic intervention in

15 nerve damage primarily by facilitating regeneration of damaged axons and regenerating nerve cells in damaged nervous system tissues.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 191 as residues: Ser-58 to His-64.

The tissue distribution in T-cells, combined with the homology to the MAL

20 and plasmolipin proteins and the detected GAS biological activity suggests that the protein product of this clone would be useful for the diagnosis and treatment of immune disorders including, but not limited to, AIDS and other immunodeficiencies. Moreover, the expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell

25 lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an

30 agent for immunological disorders including arthritis, asthma, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne,

neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus  
5 erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of  
10 various blood lineages, and in the differentiation and/or proliferation of various cell types.

The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It may also have a  
15 very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy);  
20 stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as  
25 antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 586 of SEQ ID NO:94, b is an integer of 15 to 600, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 85**

The translation product of this clone has sequence identity to a protein tyrosine kinase reported by Oates and Wilks (The Worm Breeders Gazette 14:87-87 (1995), which is hereby incorporated by reference herein). The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 2.

It has been discovered that this gene is expressed primarily in cerebellum, adult brain, retina, spinal cord, and kidney cortex.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neural, visual, and renal diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, retina, and kidney cortex. Expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, visual, renal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in cerebellum, adult brain, and spinal cord tissue suggests that the protein product of this clone would be useful for the diagnosis and treatment of neural diseases and disorders. The protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

Expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 572 of SEQ ID NO:95, b

is an integer of 15 to 586, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

## 5 FEATURES OF PROTEIN ENCODED BY GENE NO: 86

The translation product of this clone has homology to trkB, and it is thought that the protein of the present invention is a novel novel neural receptor protein-tyrosine kinase, a trkB homolog (See for example, ). This protein is likely to be derived from a gene for a ligand-regulated receptor closely related to the human trk  
10 oncogene. Northern (RNA) analysis showed that the trkB gene is expressed predominantly in the brain and that trkB expresses multiple mRNAs, ranging from 0.7 to 9 kb. Hybridization of cerebral mRNAs with a variety of probes indicates that there are mRNAs encoding truncated trkB receptors.

In specific embodiments, polypeptides of the invention comprise the sequence  
15 PCSPDPSPLPGAFVWRVLWVC (SEQ ID NO:366). Polynucleotides encoding this polypeptide are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in breast cancer, colon tumor, and B-cell lymphoma.

Therefore, nucleic acids of the invention are useful as reagents for differential  
20 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: breast cancer, colon tumor, B-cell lymphoma. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of  
25 the immune, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, gastrointestinal, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy  
30 tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 193 as residues: Ser-29 to Asn-40.

The tissue distribution in proliferative cells and tissues suggests that the protein product of this clone would be useful for the treatment, detection, and/or prevention of cancer, particularly in the indicated tissues. The expression within cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.

Alternatively, the homology to the trkB protein suggests the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal

differentiation or survival. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
10 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 788 of SEQ ID NO:96, b is an integer of 15 to 802, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 87**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ARACFAYNGVCSEGRWCDSHFHGSV (SEQ ID NO:367), MSNMGKIPSLSLHIPINKYICSRIPKFIQKVNKSTVLQICLKRQIILNKNKMSDH  
20 SKIGKANLVQIDIHSLGIVETGCVPSKRYCTLLTEQSGFPFLSHP (SEQ ID NO:368), MAGCCLKLFGVLSLCFLCGLISIERVICNPVSADFQVSTFCQRHCLLR SKVMFXIKGXTATIEVINENCTLVAAPPIGFPIXFL (SEQ ID NO:369), MSDHS KIGKANLVQIDIHSLGIVETGCVPSKRYCTLLTEQSGFPFLSHP (SEQ ID  
25 NO:370), MAGCCLKLFGVLSLCFLCGLISIERVICNPVSADFQVSTFCQRHCL LRSK (SEQ ID NO:371), VMFXIKGXTATIEVINENCTLVAAPPIGFPIXFL (SEQ ID NO:372). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in dendritic cells,  
30 and smooth muscle.



Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune, hematopoietic, and vascular diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., immune, hematopoietic, smooth muscle vascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 194 as residues: Asp-40 to Ser-52.

The tissue distribution in dendritic cells suggests that the protein product of this clone would be useful for immune disorders.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1212 of SEQ ID NO:97, b is an integer of 15 to 1226, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

## FEATURES OF PROTEIN ENCODED BY GENE NO: 88

The translation product of this gene shares sequence homology with androgen-dependant expressed protein from golden hamster hair follicles which is thought to be important in regulating the secretions from glands in the skin (See GenBank Accession No. gil191315).

5 In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: PTEGRQKVLKTFTVPRSALAMTKTSTCIYHFLVLSWYTF LNYYISQEGKDEVKPKILANGARWKY (SEQ ID NO:373), PTEGRQKVLKTF TVPRSALAMTKT (SEQ ID NO:375), PRSALAMTKTSTCIYHFLVLSWYTF LN YYISQEGK (SEQ ID NO:374), and/or FLNYYISQEGKDEVKPKILANGARWKY  
10 (SEQ ID NO:376). Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in lung, colon cancer, and testis.

Therefore, nucleic acids of the invention are useful as reagents for differential  
15 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of secretory cells including cells in the lung, colon, testis and the skin. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders  
20 of the above tissues or cells, particularly of the secretory epithelial cells in the lung, intestine, testis and skin, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,  
25 the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 195 as residues: Val-21 to Asp-30, Pro-101 to Thr-109.

The tissue distribution and homology to androgen regulated protein suggests that the protein product of this clone would be useful for treating disorders that  
30 involve highly secretory cells including those in the colon, testis, and skin. It may be useful for diagnosing disorders such as colon, lung, or testicular cancer and may be

used to treat pulmonary conditions in patients with compromised respiratory function. In addition, the polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents.

Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1106 of SEQ ID NO:98, b is an integer of 15 to 1120, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 89**

The translation product of this gene shares sequence homology with dec-205 a transmembrane protein which is thought to be important in antigen presentation in dendritic cells and T-cells.

It has been discovered that this gene is expressed primarily in macrophage, dendritic cells, lung and ulcerative colitis.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: inflammatory diseases such as ulcerative colitis. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or  
10 lower levels may be detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 196 as residues: Asp-30 to Arg-36, Gln-59 to Val-65.

The distribution in macrophage, dendritic cells, lung and ulcerative colitis tissues, and homology to antigen presenting receptors suggests that the protein product of this clone would be useful for modulating the immune response in both  
20 acute and chronic inflammatory conditions. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
25 related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
30 general formula of a-b, where a is any integer between 1 to 2582 of SEQ ID NO:99, b is an integer of 15 to 2596, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 90**

5           This gene maps to chromosome 22 and therefore polynucleotides of the present invention can be used in linkage analysis as a marker for chromosome 22.

          In specific embodiments, polypeptides of the invention comprise the sequence FKDQLVYPLLAFT (SEQ ID NO:377) and/or RQALNLPDVFGGLV (SEQ ID NO:379). Polynucleotides encoding these polypeptides are also encompassed by the  
10   invention.

          It has been discovered that this gene is expressed primarily in fetal spleen and liver as well as cd34 positive cells and to a lesser extent in several tissues suggesting a presence in blood or blood forming tissues.

          Therefore, nucleic acids of the invention are useful as reagents for differential  
15   identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: developmental defects in the blood and blood forming cells. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential  
20   identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., fetal spleen and liver as well as cd34 positive cells, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene  
25   expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

          Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 197 as residues: Gln-54 to Gly-61, Asn-79 to Leu-91, Glu-99 to Thr-105, Pro-120 to Gln-126, Pro-128 to Phe-134, Arg-150 to Arg-156, Arg-160 to Arg-170.

30           The tissue distribution in fetal spleen and liver as well as cd34 positive cells suggests that the protein product of this clone would be useful for treating disorders in

the development, proliferation, or regulation of blood forming cells including diseases such as lymphomas, granulomas, leukemias, and in the preservation and or replenishment of stem cells in the blood.

Many polynucleotide sequences, such as EST sequences, are publicly  
5 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention  
10 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1006 of SEQ ID NO:100, b is an integer of 15 to 1020, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

15

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 91**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: ATASHDLLLF (SEQ ID NO:379), MSINICLMQSKTQGSCQ  
YLLPVPVPIILKVSTVFSLLSLFRLFLSFCPPHKKCSYLLKYYGPLEGHKTLX  
20 YLRTNLGVIQPPLRMYYAAEDCNGIG (SEQ ID NO:380), MSINICLMQSKTQG SCQYLLPVPVPIILKVSTVFSLLSLFRLFL (SEQ ID NO:381), and/or SFCPPHK KCSYLLKYYGPLEGHKTLXYLRTNLGVIQPPLRMYYAAEDCNGIG (SEQ ID NO:382). Polynucleotides encoding these polypeptides are also encompassed by the invention.

25

It has been discovered that this gene is expressed primarily in T cells, fetal heart and chronic lymphocytic leukemia and to a lesser extent in kidney, lung, and 16 week embryos.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
30 diagnosis of the following diseases and conditions: disorders of the blood including abnormalities in T cell function or blood cell proliferation such as leukemia .

Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be  
5 detected in certain tissues or cell types (e.g., T cells, fetal heart and chronic lymphocytic leukemia, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

10 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 198 as residues: Leu-45 to Val-50.

The tissue distribution in T cells, fetal heart and chronic lymphocytic leukemia suggests that the protein product of this clone would be useful for treating abnormalities of the blood particularly those involving T-cells and the abnormal  
15 proliferation of blood cells such as lymphocytic leukemia. In addition, it suggests the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Moreover, the expression of this gene product suggests a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be  
20 involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an  
25 agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host  
30 diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia,

rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the expansion of stem cells and committed  
5 progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

The expression in fetal heart tissue would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. The tissue distribution in kidney  
10 suggests the protein product of this clone could be used in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe  
15 kidney, polycystic kidney, and Falconi's syndrome.

In addition, the tissue distribution in embryonic tissue suggests the protein product of this clone is useful for the diagnosis, detection, and/or treatment of developmental disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the  
20 regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders. Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell  
25 death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue  
30 differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies



directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1506 of SEQ ID NO:101, b is an integer of 15 to 1520, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

## 15 FEATURES OF PROTEIN ENCODED BY GENE NO: 92

The translation product of this gene shares sequence homology with ctg4 which is a glutamine repeat containing gene thought to be a candidate genetic disease locus.

In specific embodiments, polypeptides of the invention comprise the sequence  
 20 KEEDDDTERLPSKCEVCKLLSTE (SEQ ID NO:383 and 384) LQAELSRTGRSR  
 EVLELGQ (SEQ ID NO:385 and 386), RQAVIVCRRRFV (SEQ ID NO:387),  
 PPRWAHPKAPEGSPDPPSPPSALGLSVLPWSDSDPWHISVSPCAQREHYSPGS  
 AHINSLRPLPALSLKRCKARVSSSCLYPAPAPAPAPLEIDRCDSVPPVALCSAA  
 YTLRICWASVLCHRPPPSTSQPKPRARPKKGKAIFPTAQVP (SEQ ID NO:388),  
 25 PPRWAHPKAPEGSPDPPSPPSALGLSVLPWSDSDPWHISVSPCAQREHYSPGS  
 AHINSLRPLPALSLKRCK (SEQ ID NO:389), and/or ARVSSSCLYPAPAPAPAPL  
 EIDRCDSVPPVALCSAA YTLRICWASVLCHRPPPSTSQPKPRARPKKGKAIFPT  
 AQVP (SEQ ID NO:390). Polynucleotides encoding these polypeptides are also encompassed by the invention.

30 It has been discovered that this gene is expressed in several tissues including lung, heart, kidney, adrenal gland, smooth muscle, cerebellum, and embryonic tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: inherited developmental disorders possibly with a neuropsychiatric component. Similarly, polypeptides and antibodies  
5 directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma,  
10 urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 199 as residues: Lys-25 to Ser-36, Ser-53 to Glu-60, Thr-70 to Arg-75, Arg-111 to  
15 Thr-119, Glu-161 to Leu-189.

The tissue distribution and homology to glutamine repeat family member CTG4 suggests that the protein product of this clone would be useful for identifying and treating specific diseases related to nucleotide triplet expansion. The tissue distribution in embryonic tissue suggests the protein product of this clone is useful for  
20 the diagnosis, detection, and/or treatment of developmental disorders. The relatively specific expression of this gene product during embryogenesis suggests it may be a key player in the proliferation, maintenance, and/or differentiation of various cell types during development. It may also act as a morphogen to control cell and tissue type specification. Because of potential roles in proliferation and differentiation, this  
25 gene product may have applications in the adult for tissue regeneration and the treatment of cancers. Expression within embryonic tissue and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders.

30 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1292 of SEQ ID NO:102, b is an integer of 15 to 1306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 93**

In specific embodiments, polypeptides of the invention comprise the following amino acid sequence: EEKLFTSAPGRDFWVMGETRDGNEEN (SEQ ID NO:391). Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 16. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 16.

It has been discovered that this gene is expressed primarily in cancerous and fetal tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: cancer, developmental anomalies or fetal deficiencies. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system and developing fetus, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., developmental, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 200 as residues: Met-1 to Ser-6.

5       The tissue distribution in fetal tissue suggests that the protein product of this clone would be useful for the treatment and diagnosis of developmental anomalies or fetal deficiencies. In addition to fetal tissue, expression in a variety of cancerous tissues suggests a role in the treatment and diagnosis of uncontrolled cell proliferation and/or differentiation (e.g. cancer). Moreover, the expression within embryonic tissue  
10       and other cellular sources marked by proliferating cells suggests this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis and treatment of cancer and other proliferative disorders.

      Similarly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can  
15       result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders  
20       and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

25       Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence  
30       would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:103, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

5

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 94**

The gene encoding the disclosed cDNA is believed to reside on chromosome 10. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 10.

10 This gene is expressed primarily in hypothalamus, T-cells, and adipose tissue.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune (e.g. immunodeficiencies, autoimmunities, inflammation, leukemias & lymphomas) and neurological (e.g. Alzheimer's disease, dementia, schizophrenia) disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous, hematopoietic and immune systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., immune, neural, metabolic, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. The tissue distribution suggests that the protein product of this clone would be useful in the intervention or detection of pathologies associated with the hematopoietic and immune systems, such as anemias (leukemias). In addition, the expression in brain (including fetal) might suggest a role in developmental brain defects, neuro-degenerative diseases or behavioral abnormalities (e.g. schizophrenia, Alzheimer's, dementia, depression, etc.).

30 Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 201 as residues: Phe-64 to Gly-77, Pro-83 to Asp-99.

The tissue distribution in hypothalamus suggests the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions which include, but are not limited to Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, 5 Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in 10 feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain suggests it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. This gene product may be involved in the regulation of cytokine production, 15 antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency 20 diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue 25 injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues.

Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, this gene product may have commercial utility in the 30 expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Moreover, the protein

product of this clone is useful for the diagnosis, prevention, and/or treatment of various metabolic disorders which include, but are not limited to, Tay-Sachs disease, phenylketonuria, galactosemia, hyperlipidemias, porphyrias, and Hurler's syndrome. The protein is useful in the treatment and/or prevention of neurodegenerative conditions, particularly those which occur secondary to aberrant fatty acid metabolism (i.e. defects which affect the synthesis and integrity of the myelin sheath). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2001 of SEQ ID NO:104, b is an integer of 15 to 2015, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

#### **FEATURES OF PROTEIN ENCODED BY GENE NO: 95**

The translation product of this gene was shown to have homology to the murine leucine-rich repeat protein (See Genbank Accession No. gil2880079), which is thought to be important in neural development.

In specific embodiments, the polypeptides of the invention comprise the sequence:QKPTFALGELYPPLINLWEAGKEKSTSLKVKATVIGLPTNMS (SEQ ID NO:392). Polynucleotides encoding this polypeptide are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 7.

It has been discovered that this gene is expressed primarily in T-cells and brain.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for  
5 diagnosis of the following diseases and conditions: immunodeficiency, tumor necrosis, infection, lymphomas, auto-immunities, cancer, inflammation, anemias (leukemia) and other hematopoietic disorders, neurological diseases of the brain such as depression, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, dementia and specific brain tumors. Similarly, polypeptides and antibodies  
10 directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and immune system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, and cancerous and wounded tissues)  
15 or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO.  
20 202 as residues: Met-24 to Gly-29, Ala-57 to Thr-63.

The tissue distribution in T-cells suggests that the protein product of this clone would be useful for the diagnosis and treatment of immune disorders including: leukemias, lymphomas, auto-immunities, immunodeficiencies (e.g. AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders. In addition this  
25 gene product may be applicable in conditions of general microbial infection, inflammation or cancer. The expression in brain, combined with the homology to the leucine-rich repeat protein suggests that the protein product of this clone would be useful for the treatment and diagnosis of developmental, degenerative and behavioral conditions of the brain and nervous system, such as depression, schizophrenia,  
30 Alzheimer's disease, Parkinson's disease, Huntington's disease, Tourette Syndrome, mania, dementia, paranoia, addictive behavior, obsessive-compulsive disorder and



sleep disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are  
5 related to SEQ ID NO:105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the  
10 general formula of a-b, where a is any integer between 1 to 353 of SEQ ID NO:105, b is an integer of 15 to 367, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HKGCR51	209628 02/12/98	pSportI	11	2343	1	2343	94	94	108	1	34	35	74
2	HPMDK28	209628 02/12/98	Uni-ZAP XR	12	1177	1	1083	58	58	109	1	27	28	201
3	HLDCD04	209628 02/12/98	pCMVSPORT 3.0	13	2107	197	2107	397	397	110	1	32	33	371
3	HLDCD04	209628 02/12/98	pCMVSPORT 3.0	106	1889	1	1889	193	193	203	1	32	33	57
4	HLDON23	209628 02/12/98	pCMVSPORT 3.0	14	1262	208	1256	368	368	111	1	20	21	113
5	HLDRM43	209628 02/12/98	pCMVSPORT 3.0	15	759	1	759	164	164	112	1	20	21	151
6	HLQAM28	209628 02/12/98	Lambda ZAP II	16	1810	1	1810	43	43	113	1	36	37	55
7	HLTDE74	209628 02/12/98	Uni-ZAP XR	17	1052	1	967	106	106	114	1	20	21	236
8	HLTFA64	209628 02/12/98	Uni-ZAP XR	18	1130	1	1130	268	268	115	1	42	43	43
9	HMC FY13	209628 02/12/98	Uni-ZAP XR	19	883	1	883	175	175	116	1	30	31	64

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
10	HMMBD35	209628 02/12/98	pSport1	20	989	169	989	237	237	117	1	20	21	117
11	HMQCY03	209628 02/12/98	Uni-ZAP XR	21	495	1	495	185	185	118	1	14	15	64
12	HMSBX84	209628 02/12/98	Uni-ZAP XR	22	2317	1	2317	57	57	119	1	20	21	42
13	HMSKI86	209628 02/12/98	Uni-ZAP XR	23	1726	1	1726	84	84	120	1	24	25	47
14	HMVBS81	209628 02/12/98	pSport1	24	529	1	529	34	34	121	1	43	44	139
15	HMWEB02	209628 02/12/98	Uni-Zap XR	25	1755	1	1755	106	106	122	1	23	24	91
16	HMZAD77	209628 02/12/98	pSport1	26	1751	1	1451	49	49	123	1	34	35	346
17	HNF1Y77	209628 02/12/98	pBluescript	27	1212	28	1212	228	228	124	1	34	35	233
18	HNHEK85	209628 02/12/98	Uni-ZAP XR	28	1112	1	1112	35	35	125	1	23	24	53
19	HNHEU93	209628 02/12/98	Uni-ZAP XR	29	748	1	748	57	57	126	1	34	35	81
20	HODAH74	209628 02/12/98	Uni-ZAP XR	30	778	1	778	163	163	127	1	21	22	41

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
21	HODCU34	209628 02/12/98	Uni-ZAP XR	31	1324	1	1324	229	229	128	1	25	26	65
22	HODCZ09	209628 02/12/98	Uni-ZAP XR	32	739	9	739	225	225	129	1	43	44	49
23	HOEDB32	209628 02/12/98	Uni-ZAP XR	33	1462	73	1462	104	104	130	1	21	22	226
24	HOGAG15	209628 02/12/98	pCMVSPORT 2.0	34	2815	1	2815	411	411	131	1	17	18	117
25	HPIBO48	209628 02/12/98	Uni-ZAP XR	35	1078	1	1076	77	77	132	1	31	32	305
26	HPMFP40	209628 02/12/98	Uni-ZAP XR	36	1217	1	1217	37	37	133	1	24	25	44
27	HPRCU95	209628 02/12/98	Uni-ZAP XR	37	1282	1	1282	138	138	134	1	30	31	43
28	HPTTG19	209628 02/12/98	Uni-ZAP XR	38	559	1	559	215	215	135	1	16	17	49
29	HPTVX32	209628 02/12/98	pBluescript	39	803	215	803	318	318	136	1	27	28	80
30	HRDDV47	209628 02/12/98	Uni-ZAP XR	40	1510	1	1510	146	146	137	1	31	32	276
31	HRDEN56	209628 02/12/98	Uni-ZAP XR	41	1095	1	1095	84	84	138	1	26	27	56

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
32	HSFAN12	209641 02/25/98	Uni-ZAP XR	42	1162	1	1162	39	39	139	1	36	37	70
33	HSQCM10	209641 02/25/98	Uni-ZAP XR	43	657	1	654	130	130	140	1	19	20	62
34	HSVAT68	209641 02/25/98	Uni-ZAP XR	44	1155	1	1155	63	63	141	1	25	26	88
35	HSXEC75	209641 02/25/98	Uni-ZAP XR	45	1112	1	1112	295	295	142	1	33	34	45
36	HTDA154	209641 02/25/98	pSport1	46	4023	1	4023	37	37	143	1	37	38	55
37	HTEIT45	209641 02/25/98	Uni-ZAP XR	47	542	14	542	29	29	144	1	35	36	76
38	HTGBE48	209641 02/25/98	Uni-ZAP XR	48	1495	1	1495	169	169	145	1	18	19	42
39	HTLEP53	209641 02/25/98	Uni-ZAP XR	49	818	1	818	73	73	146	1	45	46	101
40	HTTBI76	209641 02/25/98	Uni-ZAP XR	50	1711	1	1711	133	133	147	1	22	23	133
41	HTWKG71	209641 02/25/98	Lambda ZAP II	51	749	1	749	32	32	148	1	19	20	49
42	HTXDN32	209641 02/25/98	Uni-ZAP XR	52	1091	27	804	120	120	149	1	24	25	63

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
43	HTSGX80	209641 02/25/98	pBluescript	53	2254	1	2254	19	19	150	1	20	21	74
44	HTXEY51	209641 02/25/98	Uni-ZAP XR	54	486	55	486	125	125	151	1	32	33	54
45	HTXFH55	209641 02/25/98	Uni-ZAP XR	55	1270	1	1270	61	61	152	1	40	41	57
46	HTXJW17	209641 02/25/98	Uni-ZAP XR	56	2059	1	2059	149	149	153	1	15	16	52
47	HUFCJ30	209641 02/25/98	pSport1	57	868	1	868	123	123	154	1	29	30	50
48	HWAAP70	209641 02/25/98	pCMVSPORT 3.0	58	986	1	986	26	26	155	1	33	34	66
49	HWABW49	209641 02/25/98	pCMVSPORT 3.0	59	695	1	695	170	170	156	1	23	24	48
50	HWBDP28	209641 02/25/98	pCMVSPORT 3.0	60	314	1	314	132	132	157	1	25	26	61
51	HWDAC39	209641 02/25/98	pCMVSPORT 3.0	61	734	1	734	85	85	158	1	20	21	117
52	HWHGQ49	209641 02/25/98	pCMVSPORT 3.0	62	1410	33	1410	306	306	159	1	22	23	150
53	HJPAD75	209641 02/25/98	Uni-ZAP XR	63	1231	1	1231	60	60	160	1	29	30	91

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
54	HLD RP33	209641 02/25/98	pCMVSPORT 3.0	64	612	1	612	215	215	161	1	26	27	41
55	HMSJM65	209641 02/25/98	Uni-ZAP XR	65	2270	1	2231	111	111	162	1	27	28	77
56	HNGFE55	209641 02/25/98	Uni-ZAP XR	66	1283	1	1283	132	132	163	1	15	16	54
57	HNKAA41	209641 02/25/98	pSport1	67	1263	1	1123	142	142	164	1	19	20	89
58	HRAAJ19	209641 02/25/98	pCMVSPORT 3.0	68	1617	1	1617	48	48	165	1	20	21	44
59	HSAWV96	209641 02/25/98	Uni-ZAP XR	69	1389	1	1389	278	278	166	1	24	25	44
60	HSBBT37	209641 02/25/98	pBluescript SK-	70	1896	1	1896	100	100	167	1	29	30	65
61	HSDZR57	209641 02/25/98	pBluescript	71	308	1	308	27	27	168	1	27	28	61
62	HUSIT18	209641 02/25/98	pSport1	72	1688	1	1688	343	343	169	1	24	25	46
63	HWBCP79	209641 02/25/98	pCMVSPORT 3.0	73	1138	1	1138	233	233	170	1	21	22	105
64	HYAAL70	209641 02/25/98	pCMVSPORT 3.0	74	777	1	777	88	88	171	1	41	42	44

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
65	HYAAY86	209641 02/25/98	pCMVSPORT 3.0	75	1060	1	1060	118	118	172	1	26	27	46
66	HAPBS03	209651 03/04/98	Uni-ZAP XR	76	1503	45	1479	252	252	173	1	28	29	41
67	HBJLC01	209651 03/04/98	Uni-ZAP XR	77	872	1	872	87	87	174	1	34	35	46
68	HBLKD56	209651 03/04/98	pSport1	78	573	1	573	90	90	175	1	21	22	40
69	HCENK38	209651 03/04/98	Uni-ZAP XR	79	1509	1	1509	10	10	176	1	28	29	52
70	HCHMX01	209651 03/04/98	pSport1	80	1109	1	1109	104	104	177	1	26	27	249
71	HCHNF25	209651 03/04/98	pSport1	81	807	1	807	180	180	178	1	30	31	147
72	HE6GA29	209651 03/04/98	Uni-ZAP XR	82	1043	1	1043	142	142	179	1	15	16	47
73	HE6GE84	209651 03/04/98	Uni-ZAP XR	83	1173	1	1173	334	334	180	1	14	15	55
74	HETHO95	209651 03/04/98	Uni-ZAP XR	84	1561	1	1561	309	309	181	1	24	25	48
75	HFCFJ18	209651 03/04/98	Uni-ZAP XR	85	1433	170	1433	206	206	182	1	25	26	45



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
76	HFPBM30	209651 03/04/98	Uni-ZAP XR	86	1377	1	1377	144	144	183	1	35	36	40
77	HFXKT05	209651 03/04/98	Lambda ZAP II	87	1715	1	1715	204	204	184	1	18	19	79
78	HKB1E57	209651 03/04/98	pCMVSPORT 1	88	417	1	417	30	30	185	1	26	27	46
79	HLWAD77	209651 03/04/98	pCMVSPORT 3.0	89	1167	304	1167	326	326	186	1	24	25	140
80	HLWAY54	209651 03/04/98	pCMVSPORT 3.0	90	1892	1	1892	38	38	187	1	25	26	338
81	HNGBU28	209651 03/04/98	Uni-ZAP XR	91	523	57	523	230	230	188	1	26	27	65
82	HOUHH51	209651 03/04/98	Uni-ZAP XR	92	1382	630	1296	57	57	189	1	35	36	360
82	HOUHH51	209651 03/04/98	Uni-ZAP XR	107	1201	1	815	172	172	204	1	1	2	161
83	HRAAB15	209651 03/04/98	pCMVSPORT 3.0	93	1747	1	1747	35	35	190	1	14	15	159
84	HSAVH65	209651 03/04/98	Uni-ZAP XR	94	600	1	600	104	104	191	1	24	25	100
85	HSDGN55	209651 03/04/98	Uni-ZAP XR	95	586	1	586	177	177	192	1	26	27	42

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
86	HSXAH81	209651 03/04/98	Uni-ZAP XR	96	802	1	802	88	88	193	1	21	22	61
87	HSXBX80	209651 03/04/98	Uni-ZAP XR	97	1226	1	1226	77	77	194	1	22	23	52
88	HTEHV08	209651 03/04/98	Uni-ZAP XR	98	1120	1	1120	382	382	195	1	17	18	185
89	HUFAK67	209651 03/04/98	pSportl	99	2596	1	2596	225	225	196	1	21	22	76
90	HUSXS50	209651 03/04/98	pSportl	100	1020	1	1020	179	179	197	1	23	24	174
91	HAPON17	209651 03/04/98	Uni-ZAP XR	101	1520	1	1520	266	266	198	1	23	24	50
92	HATAC53	209651 03/04/98	Uni-ZAP XR	102	1306	13	1306	99	99	199	1	21	22	189
93	HAMFK58	209641 02/25/98	pCMVSPORT 3.0	103	785	1	785	279	279	200	1	31	32	79
94	HL YCH68	209641 02/25/98	pSportl	104	2015	34	1571	81	81	201	1	19	20	105
95	HCUHK65	209641 02/25/98	ZAP Express	105	367	1	367	80	80	202	1	26	27	79

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further

below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and  
5 diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or  
10 deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or  
15 deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of  
20 plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can  
25 also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be  
30 isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed

sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the  
5 desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides  
10 produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains  
15 secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced  
20 version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural or recombinant sources using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

25

### **Signal Sequences**

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal  
30 charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the

information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, supra.) However, the two  
5 methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a  
10 protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

As one of ordinary skill would appreciate, however, cleavage sites sometimes  
15 vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely  
20 uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the  
25 naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

### 30 Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

5 By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence  
10 at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire  
15 sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known  
20 computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences  
25 are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty  
30 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95%



"identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the the

query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter

the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced  
5 for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an  
10 organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA  
15 technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after  
20 deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological  
25 activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every  
30 possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See,

Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as to have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used.

(Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

#### **Polynucleotide and Polypeptide Fragments**

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-

1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger or  
5 smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid  
10 sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-  
15 40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

20 Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the  
25 mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

30 Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and

alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.

- 5 Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

### **Epitopes & Antibodies**

- 15 In the present invention, "epitopes" refer to polypeptide fragments having antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983).)

- 20 Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

- 25 In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)



Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier-protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')<sub>2</sub> fragments) which are capable of specifically binding to protein. Fab and F(ab')<sub>2</sub> fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

### Fusion Proteins

Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous

functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., *Nature* 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See,

D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide.

- 5 In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE-vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein.
- 10 Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

15

#### **Vectors, Host Cells, and Protein Production**

- The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral
- 20 vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

- The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate,
- 25 such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

- The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac
- 30 promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The

expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography,

phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

5 Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant,  
10 insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine  
15 encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

20 In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide  
25 sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24,  
30 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al.,

Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

5

### **Uses of the Polynucleotides**

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

10 The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

15 Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids  
20 containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides  
25 can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

Precise chromosomal location of the polynucleotides can also be achieved  
30 using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however,

polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

5 For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

10 Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. 20 First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish 25 the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using 30 polynucleotides of the present invention. Any of these alterations (altered expression,

chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods  
5 rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J.  
10 Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can  
15 be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate  
20 manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel.  
25 In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA  
30 markers for RFLP.



The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using  
5 this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification  
10 techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co.  
15 (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

20 There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by  
25 organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences  
30 in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA

antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

### Uses of the Polypeptides

5           Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M.,  
10 et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such  
15 as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo  
20 imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for  
25 the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or  
30 intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety

needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of <sup>99m</sup>Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein.

- 5 In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments:" (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which  
10 involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

15 Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to  
20 activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can  
25 also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as  
30 molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also

be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

5

### **Biological Activities**

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules  
10 may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

### **Immune Activity**

A polypeptide or polynucleotide of the present invention may be useful in  
15 treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or  
20 disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in  
25 treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes  
30 include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency,

Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

5           Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood  
10           disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

15           A polynucleotide or polypeptide of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the  
20           present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

          Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic  
25           anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary  
30           Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

### 25 **Hyperproliferative Disorders**

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

### **Infectious Disease**

A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the

present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Pasteurellaceae Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis,



opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas. These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

### **Regeneration**

A polynucleotide or polypeptide of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See,

Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis,

5 reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration  
10 occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used  
15 prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a  
20 polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral  
25 neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

30

### Chemotaxis

A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

### **Binding Activity**

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable

of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a

candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

### **Other Activities**

A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

### **Other Preferred Embodiments**

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95%

identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of  
5 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of  
10 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the  
15 range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
20 sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

25 A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X  
30 in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under  
5 stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which  
10 comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide  
15 sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of  
20 at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

25 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule  
30 comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X  
5 wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and  
10 determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence  
15 selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

20 A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X  
25 wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for identifying the species, tissue or cell type of a biological  
30 sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least



one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a  
5 biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1;  
10 and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at  
15 least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise  
20 a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1  
25 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the  
30 amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in

the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence  
5 at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a  
10 polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained  
15 in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group  
20 consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least  
25 one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence  
30 selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide

comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino

acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

5 In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at  
10 least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number  
15 shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide  
20 comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

25 Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

30 Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is

expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

20

### Examples

#### Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

30

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited</u>
	<u>Plasmid</u>	
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
5	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
	pCMVSPORT 3.0	pCMVSPORT 3.0
10	pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain

XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al.,  
5 Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional  
10 plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample  
15 may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ  
20 ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with <sup>32</sup>P- $\gamma$ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular*  
25 *Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection  
30 agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for



bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the  
5 SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the  
3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired  
cDNA using the deposited cDNA plasmid as a template. The polymerase chain  
reaction is carried out under routine conditions, for instance, in 25 µl of reaction  
mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is  
10 1.5-5 mM MgCl<sub>2</sub>, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25  
pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR  
(denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1  
min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The  
amplified product is analyzed by agarose gel electrophoresis and the DNA band with  
15 expected molecular weight is excised and purified. The PCR product is verified to be  
the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding  
portions of a gene which may not be present in the deposited clone. These methods  
include but are not limited to, filter probing, clone enrichment using specific probes,  
20 and protocols similar or identical to 5' and 3' "RACE" protocols which are well  
known in the art. For instance, a method similar to 5' RACE is available for  
generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et  
al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a  
25 population of RNA presumably containing full-length gene RNA transcripts. A  
primer set containing a primer specific to the ligated RNA oligonucleotide and a  
primer specific to a known sequence of the gene of interest is used to PCR amplify  
the 5' portion of the desired full-length gene. This amplified product may then be  
sequenced and used to generate the full length gene.

30 This above method starts with total RNA isolated from the desired source,  
although poly-A<sup>+</sup> RNA can be used. The RNA preparation can then be treated with

phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction  
5 leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific  
10 to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

#### **Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

15 A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

#### **Example 3: Tissue Distribution of Polypeptide**

20 Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After  
25 labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H)  
30 or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to

manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

5     **Example 4: Chromosomal Mapping of the Polynucleotides**

          An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is  
10    repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in  
15    the particular somatic cell hybrid.

**Example 5: Bacterial Expression of a Polypeptide**

          A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA  
20    sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc.,  
25    Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

          The pQE-9 vector is digested with BamHI and XbaI and the amplified  
30    fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain

M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>).

Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250

mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further  
5 includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains:  
1) a neomycinphosphotransferase gene as a selection marker, 2) an *E. coli* origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a  
10 Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and  
XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating  
15 the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

20 The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

#### **Example 6: Purification of a Polypeptide from an Inclusion Body**

The following alternative method can be used to purify a polypeptide  
25 expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit  
30 weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM

Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate  
5 is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the  
10 pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA  
15 by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The  
20 filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

25 Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40  
30 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium

acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5  $\mu$ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

#### **Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System**

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in

Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in  
5 Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment  
10 then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a  
15 commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified  
20 by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five  $\mu$ g of a plasmid containing the polynucleotide is co-transfected with 1.0  $\mu$ g of a commercially available linearized baculovirus DNA ("BaculoGold™  
25 baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One  $\mu$ g of BaculoGold™ virus DNA and 5  $\mu$ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50  $\mu$ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10  $\mu$ l Lipofectin plus 90  $\mu$ l Grace's medium are  
30 added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded



in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

- 5       After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell
- 10   culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded
- 15   in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

- To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of
- 20   infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of <sup>35</sup>S-methionine and 5 µCi <sup>35</sup>S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation.
- 25   The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

30   **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIV and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human HeLa, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a

chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession  
5 No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the  
10 polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

15 A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

20 The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and  
25 purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for  
30 transfection. Five  $\mu$ g of the expression plasmid pC6 is cotransfected with 0.5  $\mu$ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo

contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1  $\mu$ M, 2  $\mu$ M, 5  $\mu$ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200  $\mu$ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

#### 15 **Example 9: Protein Fusions**

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

30 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These

primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAACTCACACATGCCCACCGTGCCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

**Example 10: Production of an Antibody from a Polypeptide**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is

possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody  
5 whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')<sub>2</sub> and other fragments of the  
10 antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic  
15 chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in  
20 the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

25

#### **Example 11: Production Of Secreted Protein For High-Throughput Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in  
30 Examples 13-20.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at  $2 \times 10^5$  cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.



While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl<sub>2</sub> (anhyd); 0.00130 mg/L CuSO<sub>4</sub>·5H<sub>2</sub>O; 0.050 mg/L of Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O; 0.417 mg/L of FeSO<sub>4</sub>·7H<sub>2</sub>O; 311.80 mg/L of KCl; 28.64 mg/L of MgCl<sub>2</sub>; 48.84 mg/L of MgSO<sub>4</sub>; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO<sub>3</sub>; 62.50 mg/L of NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O; 71.02 mg/L of Na<sub>2</sub>HPO<sub>4</sub>; 4320 mg/L of ZnSO<sub>4</sub>·7H<sub>2</sub>O; .002 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H<sub>2</sub>O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H<sub>2</sub>O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H<sub>2</sub>O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H<sub>2</sub>O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B<sub>12</sub>; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

5 On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the  
10 polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

#### 15 **Example 12: Construction of GAS Reporter Construct**

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The  
20 binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in  
25 many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus  
30 upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2,

Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, *Ann. Rev. Biochem.* 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

254

<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u> <u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>	<u>STATS</u>	<u>GAS(elements) or ISRE</u>
<u>IFN family</u>						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g	+	+	+	-	1	GAS (IRF1>Lys6>IFP)
IL-10	+	?	?	-	1,3	
<u>gp130 family</u>						
IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
IL-11(Pleiotrophic)	?	+	?	?	1,3	
OnM(Pleiotrophic)	?	+	+	?	1,3	
LIF(Pleiotrophic)	?	+	+	?	1,3	
CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrophic)	?	+	?	?	1,3	
IL-12(Pleiotrophic)	+	-	+	+	1,3	
<u>g-C family</u>						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
<u>gp140 family</u>						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
<u>Growth hormone family</u>						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
<u>Receptor Tyrosine Kinases</u>						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

SUBSTITUTE SHEET (RULE 26)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCC  
GAAATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAA  
TGATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCG  
CCCCTAACTCCGCCCATCCCGCCCCCTAACTCCGCCCAGTTCCGCCCATTCT  
CCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCC  
TCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCT  
AGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

25

### **Example 13: High-Throughput Screening Assay for T-cell Activity.**

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells

30

(ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1% Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells ( $10^7$  per transfection), and resuspend in OPTI-MEM to a final concentration of  $10^7$  cells/ml. Then add 1ml of  $1 \times 10^7$  cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

5 After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

10 The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source  
15 of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

20 The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

#### **Example 14: High-Throughput Screening Assay Identifying Myeloid Activity**

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate  
25 myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

30 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell



Growth & Differentiation, 5:259-265) is used. First, harvest  $2 \times 10^7$  U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

5        Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM  $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$ , 1 mM  $\text{MgCl}_2$ , and 675 uM  $\text{CaCl}_2$ . Incubate at  $37^\circ\text{C}$  for 45 min.

10        Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at  $37^\circ\text{C}$  for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

15        These cells are tested by harvesting  $1 \times 10^8$  cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of  $5 \times 10^5$  cells/ml. Plate 200 ul cells per well in the 96-well plate (or  $1 \times 10^5$  cells/well).

20        Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at  $37^\circ\text{C}$  for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

#### **Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

25        When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat pheochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor).

- 5 The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene  
10 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified  
15 product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30  
20 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-  
25 inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine  
30 protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine

growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS  
5 (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing ~~1% horse serum and 0.5% FBS~~ with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as  $5 \times 10^5$   
10 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to  $1 \times 10^5$  cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold  
15 induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

#### **Example 16: High-Throughput Screening Assay for T-cell Activity**

NF- $\kappa$ B (Nuclear Factor  $\kappa$ B) is a transcription factor activated by a wide  
20 variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- $\kappa$ B regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- $\kappa$ B appears to shield cells from apoptosis), B and T-cell development,  
25 anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- $\kappa$ B is retained in the cytoplasm with I- $\kappa$ B (Inhibitor  $\kappa$ B). However, upon stimulation, I- $\kappa$ B is phosphorylated and degraded, causing NF- $\kappa$ B to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- $\kappa$ B include IL-2, IL-6, GM-CSF, ICAM-1 and  
30 class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- $\kappa$ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- $\kappa$ B would be useful in treating diseases. For example, inhibitors of NF- $\kappa$ B could be used to treat those diseases related to the acute or chronic activation of NF- $\kappa$ B, such as rheumatoid arthritis.

To construct a vector containing the NF- $\kappa$ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- $\kappa$ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:  
5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGAC  
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGACTTTCC  
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC  
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA  
CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCTCGGCCTCTGAGCTA  
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA  
GCTT:3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2- promoter plasmid (Clontech) with this NF- $\kappa$ B/SV40 fragment using XhoI and

HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- $\kappa$ B/SV40/SEAP cassette is removed from the above NF- $\kappa$ B/SEAP vector using restriction enzymes  
5 SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF- $\kappa$ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF- $\kappa$ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly,  
10 the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

#### **Example 17: Assay for SEAP Activity**

15 As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15  $\mu$ l of 2.5x  
20 dilution buffer into Optiplates containing 35  $\mu$ l of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50  $\mu$ l Assay Buffer and incubate at room  
25 temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50  $\mu$ l Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

30 Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

**Reaction Buffer Formulation:**

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

**Example 18: High-Throughput Screening Assay Identifying Changes in Small****5 Molecule Concentration and Membrane Permeability**

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants

which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

5           The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

10           For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO<sub>2</sub> incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

          A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To  
15       load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37°C in a CO<sub>2</sub> incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

          For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10<sup>6</sup> cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml  
20       fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10<sup>6</sup> cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed  
25       once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

          For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

          To measure the fluorescence of intracellular calcium, the FLIPR is set for the  
30       following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm;

and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular  $\text{Ca}^{++}$  concentration.

5 **Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity**

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St.



Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar

- 5 Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyn Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

- To prepare extracts, A431 cells are seeded onto the nylon membranes of
- 10 Loprodyn plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na<sub>3</sub>VO<sub>4</sub>, 2 mM
- 15 Na<sub>4</sub>P<sub>2</sub>O<sub>7</sub> and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well
- 20 catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4°C at 16,000 x g.

- Test the filtered extracts for levels of tyrosine kinase activity. Although many
- 25 methods of detecting tyrosine kinase activity are known, one method is described here.

- Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include
- 30 PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and

PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg<sub>2</sub><sup>+</sup> (5mM ATP/50mM MgCl<sub>2</sub>), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initiate the reaction by adding 10ul of the control enzyme or the filtered supernatant.

10 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide.

15 Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.

20 Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

#### 25 **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**

As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine

30

phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

**Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim); and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv.

et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

**Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample**

10 A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

15 For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

25 Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

30 Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard

curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

5

**Example 23: Formulating a Polypeptide**

The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1  $\mu\text{g/kg/day}$  to 10  $\text{mg/kg/day}$  of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01  $\text{mg/kg/day}$ , and most preferably for humans between about 0.01 and 1  $\text{mg/kg/day}$  for the hormone. If given continuously, the secreted polypeptide is typically administered at a dose rate of about 1  $\mu\text{g/kg/hour}$  to about 50  $\mu\text{g/kg/hour}$ , either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's

solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical



compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the

5 polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

**Example 24: Method of Treating Decreased Levels of the Polypeptide**

It will be appreciated that conditions caused by a decrease in the standard or

10 normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to

15 increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

20

**Example 25: Method of Treating Increased Levels of the Polypeptide**

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as

25 cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense

30 polynucleotide is provided in Example 23.

**Example 26: Method of Treatment Using Gene Therapy**

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and  
5 separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS,  
10 penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

15 pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified  
20 using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions  
25 appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with  
30 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector.

The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

#### **Example 27: Method of Treatment Using Gene Therapy - In Vivo**

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) Cardiovasc. Res. 35(3):470-479, Chao J et al. (1997) Pharmacol. Res. 35(6):517-522, Wolff J.A. (1997) Neuromuscul. Disord. 7(5):314-318, Schwartz B. et al. (1996) Gene Ther. 3(5):405-411, Tsurumi Y. et al. (1996) Circulation 94(12):3281-3290 (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection

into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

#### **Example 28: Transgenic Animals.**

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, e.g., baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-

mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones  
5 containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene  
10 in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory  
15 sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is  
20 to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only  
25 that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the  
30 recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA

expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also  
5 be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more  
10 than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for  
15 screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not  
20 limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

#### 25 **Example 29: Knock-Out Animals.**

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by  
30 reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding



regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, *e.g.*, by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, *e.g.*, in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and  
5 Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For  
10 example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological  
15 function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

It will be clear that the invention may be practiced otherwise than as  
20 particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other  
25 disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entirety.

## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>180</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>February 12, 1998</u>	Accession Number <u>209628</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only
<input checked="checked" type="checkbox"/> This sheet was received with the international application
<u>C. Williams</u>
Authorized officer

For International Bureau use only
<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer

## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>183</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>February 25, 1998</u>	Accession Number <u>209641</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only
<input checked="" type="checkbox"/> This sheet was received with the international application
<u>C. Williams</u>
Authorized officer

For International Bureau use only
<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer

## INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

<b>A.</b> The indications made below relate to the microorganism referred to in the description on page <u>186</u> , line <u>N/A</u>	
<b>B. IDENTIFICATION OF DEPOSIT</b> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>March 4, 1998</u>	Accession Number <u>209651</u>
<b>C. ADDITIONAL INDICATIONS</b> (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
<b>D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE</b> (if the indications are not for all designated States)	
<b>E. SEPARATE FURNISHING OF INDICATIONS</b> (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	
<input checked="" type="checkbox"/> This sheet was received with the international application	
<u>C. Williams</u>	
Authorized officer	

For International Bureau use only	
<input type="checkbox"/> This sheet was received by the International Bureau on:	
Authorized officer	

***What Is Claimed Is:***

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group  
5 consisting of:
  - (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a  
10 polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - 15 (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
  - (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X,  
20 having biological activity;
  - (f) a polynucleotide which is a variant of SEQ ID NO:X;
  - (g) a polynucleotide which is an allelic variant of SEQ ID NO:X;
  - (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
  - 25 (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.

5 3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

10 4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

15 5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

20 6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

25

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

30

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

- 5 (a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;
- (c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- 10 (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- (f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;
- 15 (g) a variant of SEQ ID NO:Y;
- (h) an allelic variant of SEQ ID NO:Y; or
- (i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

25

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

- 30 (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and



(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

5 17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

10 18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

15

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

20 (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

25 (a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

30

22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- 5 (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

<110> Human Genome Sciences, Inc., et al.

<120> 95 Human Secreted Proteins

<130> PZ027PCT

<140> Unassigned

<141> 1999, March 18

---

<150> 60/078,566

<151> 1998-03-19

<150> 60/078,574

<151> 1998-03-19

<150> 60/078,576

<151> 1998-03-19

<150> 60/078,563

<151> 1998-03-19

<150> 60/078,573

<151> 1998-03-19

<150> 60/078,578

<151> 1998-03-19

<150> 60/078,579

<151> 1998-03-19

<150> 60/078,581

<151> 1998-03-19

<150> 60/078,577

<151> 1998-03-19

<150> 60/080,314

<151> 1998-04-01

<150> 60/080,312

<151> 1998-04-01

<150> 60/080,313

<151> 1998-04-01

<160> 392

<170> PatentIn Ver. 2.0

<210> 1

<211> 733

<212> DNA

<213> Homo sapiens

<400> 1

```

gggatccgga gcccaaattct tctgacaaaa ctcacacatg cccaccgtgc ccagcacctg      60
aattcgaggg tgcaccgtca gtcttcctct tcccccaaaa acccaaggac accctcatga      120
tctcccgga ccttgaggtc acatgcgtgg tgggtggacgt aagccacgaa gaccctgagg      180
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg      240
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact      300
ggctgaattg caaggagtac aagtgcgaag tctccaacaa agccctccca acccccatcg      360
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acagggtgtac accctgcccc      420
catcccgga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct      480
atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga      540
ccacgcctcc cgtgctggac tccgacggct ccttcttctc ctacagcaag ctcaccgtgg      600
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc      660
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgagtg cgacggccgc      720
gactctagag gat                                     733

```

&lt;210&gt; 2

&lt;211&gt; 5

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; Site

&lt;222&gt; (3)

&lt;223&gt; Xaa equals any of the twenty naturally occurring L-amino acids

&lt;400&gt; 2

Trp Ser Xaa Trp Ser

1

5

&lt;210&gt; 3

&lt;211&gt; 86

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 3

```

gcgccctcag atttccccga aatctagatt tccccgaaat gatttccccg aaatgatttc      60
cccgaatat ctgccatctc aattag                                     86

```

&lt;210&gt; 4

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 4

gctgcaagct ttttgcaaag cctaggg

27

&lt;210&gt; 5

&lt;211&gt; 271

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 5

ctcgagattt cccccgaaatc tagatttccc cgaaatgatt tccccgaaat gatttccccg

60

aaatatctgc catctcaatt agtcagcaac catagtcccg cccctaactc cgcccatccc	120
gcccctaact ccgcccagtt ccgcccattc tccgccccat ggctgactaa ttttttttat	180
ttatgcagag gccgaggccg cctcggcctc tgagctattc cagaagtagt gaggaggctt	240
ttttggaggc ctaggctttt gcaaaaagct t	271

<210> 6  
 <211> 32  
 <212> DNA  
 <213> Homo sapiens

<400> 6	
gcgctcgagg gatgacagcg atagaacccc gg	32

<210> 7  
 <211> 31  
 <212> DNA  
 <213> Homo sapiens

<400> 7	
gcgaagcttc gcgactcccc ggatccgcct c	31

<210> 8  
 <211> 12  
 <212> DNA  
 <213> Homo sapiens

<400> 8	
ggggactttc cc	12

<210> 9  
 <211> 73  
 <212> DNA  
 <213> Homo sapiens

<400> 9	
gcggcctcga ggggactttc ccggggactt tccggggact ttccgggact ttccatcctg	60
ccatctcaat tag	73

<210> 10  
 <211> 256  
 <212> DNA  
 <213> Homo sapiens

<400> 10	
ctcgagggga ctttcccggg gactttccgg ggactttccg ggactttcca tctgccatct	60
caattagtca gcaaccatag tcccggccct aactccgcc atccccccc taactccgcc	120
cagttccgcc cattctccgc cccatggctg actaattttt tttatttatg cagaggccga	180
ggccgcctcg gcctctgagc tattccagaa gtagtgagga ggcttttttg gaggcctagg	240
cttttgcaaa aagctt	256

<210> 11  
 <211> 2343  
 <212> DNA  
 <213> Homo sapiens

<400> 11  
 acgcgtccgg tttttcaaag gtttaactgt ccagggcaga tacttaagac tatctgatca 60  
 tccattaaaa acttttcaca tagtcttgct taaatggatc cattatgttt acccattata 120  
 ttgttctcag ctgtagtttt aagaaattta tttcatttgt taatacttac tttccattac 180  
 cttccccttt tctgtgacaa tccgttgata cttgaagacc tctcttgat tcatcttagg 240  
 gttaatatatt ttaaggccaa acagcctaaa ttctatggta atcaactcca gccttggtga 300  
 atgaaatctt ctgcataaag atagggttaa atcaaatcag attgcagatt ttattgaaga 360  
 aatttgtgttt ttaagagttg acaaatatat gttgtatggc taaaacaaag aaaatacttc 420  
 tgttgcttct gcatttagta gaagaaaaac tatatatgtt tgtgaccaa gtataaaata 480  
 tgattctttc cagggaggta aaggttatgc acaagatttt cactagcagc tctaaaaggc 540  
 taccctcaat taattgccat gaacatttca tagccctaga aggatgtagg ctcatctcag 600  
 tgtcatcctg gtttattctt tattgtatta ttcagcagtc attttaacac tatgctagac 660  
 acttttagaga ttcagaagag taacagggtt tctgttctca tgaagcttat caggagacag 720  
 aaaacatatg aattagatct aattggaggc aaactgaaat atatagtgga gttagtgtgg 780  
 ttatcagcac ataaatgagt gatccatcaa caaaggaga aattgggagg gttttatggg 840  
 caaaaaacag catgattaaa tgtgatagag tatatgtcat gttttagggtg tgatgaacat 900  
 tcagttatgt gtgacgaata ggataattga aaaaatatga aaggctatga tgccagaaag 960  
 tattatggga caagatctta aaaccagtgt tacttaggga gtatgaattt aatatgggaa 1020  
 ttcttaaaact cctttatgac tggaagatga gcatcagagt gtctgcgacc attttgatga 1080  
 tatgatgtac cagtttttaa atgtttggct ttttccaggt gatgaaagcg ggggatgagt 1140  
 taagaaccac tgctgtgaag gattcacaac tatttttagg cagttgggta aaaatgacca 1200  
 attttagtttt aagaaaactga ctgtggctcc agagtatgtt ggagaagtga aaatggagac 1260  
 taggaataac aggtgggaga ctattagtct aattaagatg taattataaa tctaagctag 1320  
 gaacgtaaaa tgagaatgca aagtaagaaa caaatatggg gaaaattata tgtaaaagta 1380  
 ataggacttg gcatcttact gatgtgattg attatgagaa aaatgaagca tgtggaggag 1440  
 tccactggac agtaggaaat tcagcctaag acttgggtaa gagttctgtg gagttgtgaa 1500  
 ttcagaggcc agagatgtga tatttaaaat tttggttcaa gatttcccag gtataagaaa 1560  
 gcaagaggat taaagcattg taattaaact ttaagcagt catatttatg ttatagataa 1620  
 gataaacaag aaatctaggg atcaaatagg attaaaatta gtagtgatca ttcagtacag 1680  
 tagttacgta ctgttattca caagagtata taaatcaaat tacaaggaat taaggatata 1740  
 aacgtgataa gaaagtatgc actgtactct ttgaggaagt ttgccataga aaggaagaag 1800  
 aaataggatg gtagatcaga agtaaagcag gaccagtggt ggggagtgtt tgcagtgagg 1860  
 cagtatgtat aatcatttaa aacatgggtt tggagtcctc tcaggttcca tgtttgtaat 1920  
 ggacataatg ataataatcc ctttcattta aggctgtgtg gaggattaaa tgtgttaatg 1980  
 tgcaataaac ttacacagt gcctgggtata taataaatgc ttgctaccta ttaactagta 2040  
 tttgtttcta aggtcaattt aagtcctaga attgattgca aggattagat caggagtata 2100  
 gtggacatgt tgggatttaa atatttaa atagagatgc tttttaggac cattgttaga 2160  
 accagaagag attttttacc aagttcacac agaaatgtag gtgcattggc tgggcatggt 2220  
 ggctcacacc tgcagtccca gcacttggga aggctgaggc agaagaactg cttgaggcca 2280  
 acattttgag accagcctgg gcaacatatt aagaccccg ctccaccaa aaaaaaaaaa 2340  
 aaa 2343

<210> 12  
 <211> 1177  
 <212> DNA  
 <213> Homo sapiens

<220>

<221> SITE  
 <222> (1095)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1115)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1142)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1162)  
 <223> n equals a,t,g, or c

<400> 12  
 agccaccatg cccggcctag attaaaaaatt tgaagacata ttctctacta tgagccaatg 60  
 aaattactca ttttgtttct atcccatttg ctgtcccttg cttttggaat tttgtgtctt 120  
 agtgtgactg tgattctttc tctccttttg tctttcagca aacgggggatt cagcgtccga 180  
 tcctttggaa cagggactca cgtgaagctt ccaggaccag ctcccgacaa gcccaatggt 240  
 tatgatttca aaaccacata tgaccagatg tacaatgatc ttcttaggaa agacaaagaa 300  
 ctctatacac agaatgggat tttacatatg ctggacagaa ataagagaat caagccccgg 360  
 ccagaaagat tccagaactg caaagacctg tttgatctga tcctcacttg cgaagagaga 420  
 gtgtatgacc aggtggtgga agatctgaat tccagagAAC aggagacctg ccagccygtg 480  
 cacgtgggtca atgtggacat ccaggacaac cacgaggagg ccaccctggg ggcgtttctc 540  
 atctgtgagc tctgccagtg tatccagcac acggaagaca tggagaacga gatcgacgag 600  
 ctgctgcagg agttcgagga gaagagtggc cgcacctttc tgcacaccgt ctgcttctac 660  
 tgagcccagc gcccgcatgg agccgcctct ggagcttctt gttgttcata ctttttcctt 720  
 cctgacattt gtttttactt acagggtgtt tgctggtgac ggtagcatta cccaaataaa 780  
 ctgtgcataat gaaatgggag aggagatgcc aaaacgccag atgaaagcaa tcaagtttct 840  
 tcttttccac ttttacttat gagcrggata ttgattacaa agtttttctt ctttaaccaa 900  
 aaaggaaaga caacggtttg tgtgcacttc ccgacatacc tgtgtcttcg tgtgcctgcc 960  
 ttccctccct cctccccacc gggccggact gtacagagcc ctgctgcggc gtgttaggaa 1020  
 tgacctggaa ttgtcaataa acagatgctg ctgtcaaaaa aaaaaaaaaa aaaaaaaaaa 1080  
 aaaaaaaaaa raaancaaaa aaaaaaaaaa aaggnggggc cgaagggtttt ttcccttttg 1140  
 tnggggttat ttttggttg gnattggcct tcgtttt 1177

<210> 13  
 <211> 2107  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (149)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (487)

<223> n equals a,t,g, or c

<400> 13

tttaggtatg	catataaaaag	aaaacaaaat	atttaaaaaca	cttaaaggag	atctgacgaa	60
acctaaagag	aagaaaaata	ataaaattaa	gtaaagaaaw	ggtatggcag	gattttatgt	120
ttgcctgtgc	cctttatcca	actgatcang	gcttcctgga	wtcagtgaca	gcagaagttg	180
cctaccagat	caagagactg	aaatctcatc	cttctatcat	catatggagt	ggcaataatg	240
aaaatgagga	ggcgctgatg	atgaattggt	atcatatcag	tttcaactgac	cggccaatct	300
acatcaagga	ctatgtgaca	ctctatgtga	aaaacatcag	agagctcgta	ctggcaggag	360
acaagagtcg	tccttttatt	acgtccagtc	ctacaaatgg	ggctgaaact	gttgacagaag	420
cctgggtctc	tcaaaaccct	aatagcaatt	attttgggtga	tgtacatttt	tatgactata	480
tcagtgntat	gctggaactg	gaaagttttc	ccaaaagctc	gattttgcac	tgaatatgga	540
tatcagtcct	ggccgctcct	cagtacatta	gaaaaggtct	cgtctacaga	ggactggtct	600
ttcaatagca	agttttcact	tcacgcagaa	catcacgaag	gtggttaaca	acaaatgctt	660
tatcaggctg	gacttcattt	caaactcccc	caaagcacag	atccattacg	cacattttaa	720
gataccatct	accttactca	ggtgatgcag	gccagtggtg	tcaaaacaga	aactgaattc	780
taccgccgta	gtcgcagcga	gatagtggat	cagcaagggc	acacgatggg	ggcactttat	840
tggcagttga	atgacatctg	gcaagctcct	tcctgggctt	ctcttgagta	cggaggaaaag	900
tggaaaatgc	ttcattactt	tgctcagaat	ttctttgctc	cactgttgcc	agtaggcttt	960
gagaatgaaa	acaygttcta	tatctatggt	gtgtcagatc	ttcactcgga	ttattcgatg	1020
acactcagtg	tgagagtcca	tacatggagc	tcctgggagc	ccgtgtgctc	tcgtgtgact	1080
gaacgttttg	tgatgaaagg	aggagaggct	gtctgccttt	atgaggagcc	agtgtctgaa	1140
ttgctgagga	gatgtgggaa	ttgcacacgg	gaaagctgtg	tggtttcctt	ttacctttca	1200
gctgaccatg	aactcctgag	cccgaaccaac	taccatttcy	tgctctcacc	gaaggaggcc	1260
gttggggctct	gcaaggcgca	gatcactgcc	atcatctctc	agcaagggtga	catatttggt	1320
tttgacctgg	agacctcagc	tgctcgctccc	tttgtttggt	tggatgtagg	aagcatecca	1380
gggagattta	gtgacaatgg	tttctctcatg	actgagaaga	cacgaactat	attatttttac	1440
ccttggggagc	ccaccagcaa	gaatgagttg	gagcaatctt	ttcatgtgac	ctccttaaca	1500
gatattttact	gaaggaatct	aggttgtatt	ttcagtggac	aatgggaata	aagcatttct	1560
aaagcaccga	ctggagagga	aggcaacaga	gacaaggaga	gaagccgaga	gacatgtctg	1620
cgtgctgcca	cgcactctgag	cgattgctct	gtgaagagtt	gtacactgaa	catttttcagg	1680
ggaggctggt	taccagggca	atgtcctcaa	acaagcctgt	gccgggggtgt	cctggaatct	1740
gtgccaggac	tgtgttttta	gcccttcacc	tctcagcttt	agcaggacat	gaaccagtta	1800
taacaagatg	sccttcgcagc	tggttacaag	aatgtgacat	ggcaggatct	atggaaccaa	1860
atggaagggt	ttgagggtgat	gtaggctctt	cacagttagc	tttgggggaat	acagaatact	1920
caaataaagt	gctttgttat	tatttcagag	ggaatggcga	ttgaaatgtt	acaacagaga	1980
tttcttggtg	gtagctattt	gggtaaaggt	atatggatat	ttttctgtac	atgtgaaatt	2040
atataaaaat	aaaagttata	taaattacat	tgaaaaaaaaa	aaaaaaaaaaa	aaaaaaaaagg	2100
cggccgc						2107

<210> 14

<211> 1262

<212> DNA

<213> Homo sapiens

<400> 14

cctaattggcc	cgasctgaat	acttgaagga	gctcaagatg	agggaatctc	gctgggaagc	60
tgacaccctg	gacaaagagg	gactgtcgga	atctgttcgt	agctcttgca	cccttcagtg	120
accctagaag	aatgattgga	cagatgtgag	ccatctggag	cagaggggca	ctaaccagg	180
ctgacgccaa	gaatgaagtg	gccactgca	gccctggcga	gcaggcttct	tggatggaca	240
gtgctgagac	ccccatatcc	cagagtcccc	agcctccctc	aggttactct	gcacccaca	300
gatggtttga	tggctgtgct	gtatactgga	ggggagggca	ggactctggg	agaacagcac	360
ttctttcatg	agacctttgt	tactcgggtg	ttactgggtc	ctgtgcctgt	ccgttttggg	420
gcattgcagcc	ctctatcatt	tttggctccg	agaagagggc	aagggggcccc	cgcagggtarc	480



ttctgtgctt	gccctcgccc	tgccagcagg	cagctgtgcc	cctggcctgc	ccttcccggg	540
accccttatt	ccaactcagc	tcctctttgc	actggaatgg	ggcactccaa	caccctcag	600
ggaccacctt	ccccacagta	tgcactcagc	cccacagaac	ccaccagtct	ttctgggaac	660
tcacacctgc	cgcctatctt	ggtactttag	gttaatccct	caagcatgaa	agctggatct	720
tttgggggtt	aagaagccca	agccttggtc	ctgccctggc	ctagggagca	ctcaggaggg	780
ttccttggtc	ctcatctctc	ccacctccgt	tcctctctgg	ccccacacta	gccacagcgc	840
gggccttggtg	ctggagtttg	agcctgggac	agggagaggg	aggcttgagg	acagtctgac	900
ccagtgcctt	ctaggccacc	cacttctagg	cctgccctgc	cgccgtggag	ccctgggcaa	960
gctctttccc	ctttctgggc	ctgggtctcc	ccatctcttc	aatggggctg	ataccttcac	1020
agcccacagc	atgggcactt	atgaggacaa	agtgaattta	acctggaaaa	gaatgtatct	1080
gagagtttct	tttaaataat	cagcgggtgt	tggtgatttg	tagcccttct	gcccttaaata	1140
gcttccttgg	gcaagagctg	tctgtcctcc	ctgcaggagg	ctgagtggtg	agagtatcat	1200
tcattgtttc	tctattaaat	tattttctgc	taaaaaaaaa	aaaaaaaaaat	ttctgcggtc	1260
cg						1262

<210> 15  
 <211> 759  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (16)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (22)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (36)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (51)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (52)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (57)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (58)  
 <223> n equals a,t,g, or c

&lt;400&gt; 15

ggattaacaa	attnncaca	cnaggaaaac	aggtnnttga	cccaattagg	nnttttnnca	60
aaaaagctta	tttttaggtt	gacacttatt	agaagttacg	ccttgacagg	taccgggtcc	120
ggaattcccg	ggtcgaaccc	caaggggttc	gcggacccca	gacatgagga	ggctcctcct	180
ggtcaccagc	ctggtggttg	tgctgctgtg	ggaggcagg	gcagtcccag	cacccaagg	240
ccctatcaag	atgcaagtca	aacactggcc	ctcagagcag	gacccagaga	aggcctgggg	300
cgcccggtg	gtggagcctc	cggagaagga	cgaccagctg	gtggtgctgt	tcctgttcca	360
gaagccgaaa	ctcttgacca	cggaggagaa	gccacgaggt	cagggcagg	gccccatcct	420
tccaggcacc	aaggcctgga	tggagaccga	ggacaccctg	ggcgtgtcc	tgagtcccg	480
gcccagccat	gacagcctgt	accaccctcc	gcctgaggag	gaccagggcg	aggagaggcc	540
ccggttggtg	gtgatgccaa	atcaccagg	gctcctggga	ccggagggaag	accaagacca	600
catctaccac	ccccagtagg	gtccagggg	ccatcactgc	ccccgccctg	tccaaggcc	660
caggctgttg	ggactgggac	cctccctacc	ctgccccagc	tagacaaata	aacccagca	720
ggccgggaaa	aaaaaaaaa	aaaaaaaaa	ggcggccgc			759

&lt;210&gt; 16

&lt;211&gt; 1810

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 16

cacgagggtg	tgctgtctta	ggcaggaacc	cagttttact	ttatgccatg	tggaaagttt	60
ctttttccag	tatcaccagt	gagttcactg	tctctccact	ggtctgcagt	gctgcttctg	120
ttacttgcag	acttcccacg	tgtgcatgga	tctccacctg	gggtctctag	ggtctctatt	180
ctacactgcc	tatttccctt	tctgtcctaa	caccatagca	tttaactcac	ccgtcatcct	240
gtgttgctga	gaatttcctt	catagaactc	atcaaagtat	gattaactgt	gctccctgag	300
ggcaggaatt	atgccatctg	gatcaccagc	ctctcccttg	tccttagcac	gccatctgca	360
aattagcaga	tactcggtaa	atgtgtatta	actcgaagta	tattttgtgt	cttctctgtg	420
cacagcactg	ccctgggaag	aactaggatg	aggatttgac	ttgctgttgc	cacataacaa	480
accctgccag	aactccctgg	atggaagtga	ccaccgtgta	tctgtggatt	gtctgcagg	540
ctctgctggg	gtcagcagg	cccacaacag	agccagggtc	cggctctctc	atggctgtca	600
gaggtttacg	tattccgcct	cctcccacca	aagtctgaag	ttgttgatt	ccattccttg	660
ctatatccac	atcttttaat	aatgctaaaa	tcccgtgttt	ctctaaagca	ttggattgaa	720
ccaactgaag	aaggaccacg	tgtgttgctg	ggcctgcttg	ggcacaagcc	gtttccgac	780
caagtcaact	gctggtctgc	ttagacgaag	gtgtgtgggt	gtctccacca	cggagaggag	840
ggacagcagg	tgagaccata	ggccaggaag	gaagggcaca	gcctaagcgt	gcagtggctt	900
agccagagac	cctcgtgcac	cagccttcca	ggtgcttatt	ggaacttatg	tcagcccagg	960
ccatatccaa	gtgtgtgatg	tctcggagca	tatatgccag	gccagccgga	gaggcttagc	1020
cctgccctgg	tggagctgga	gggcccagag	gcccgcgggt	ggggtcagga	ggttgtgaag	1080
aggatcctga	tacaggctgg	gcctccctgc	aggcgtgagc	cccggagcac	ggggtgagca	1140
gctccaccca	gaggggcttg	caggaccaag	ctgggacagc	aaccaccagg	ccctggggca	1200
gatcagtgag	cgtccaggag	atgcagatgc	agaagacagc	caaattcatt	cacctctgcg	1260
tgggcctgtg	agggcccaca	gagatgcatt	ttcattcacg	accaggattt	cctcggccgg	1320
agcagccgct	tttcccagcc	gaagctcact	gtgtttacta	cataggatgt	gagtgtatag	1380
aaagactctc	tctaacgtta	gtacgcgtgc	agaaatgtgg	ggccgcttac	aagtgtgggc	1440
agccgcagcc	tgttcctcac	ccctgtccta	acgggacata	ctccacgcat	gcacatttag	1500
gatcaccgtg	tcttctcggt	ggactgatct	gtcattagga	ccctggaccc	aagtaattgt	1560
ctttgctctg	aagttttgac	agtaacaaag	gcattccagc	tctttctttt	tactcctgt	1620
cgggtgtaacg	tgccgttttt	catectttga	cttttagccc	gcctgtgccc	tgtctgaagg	1680
gagttgtctg	tggacagtca	cggagtggtg	ggtgtttgta	atccactctg	ccagcctcag	1740
tcttctaact	gttgcgatag	gaccaattac	atctgccctt	tctcttccct	gctaaaaaaaa	1800
aaaaaaaaaa						1810

<210> 17  
 <211> 1052  
 <212> DNA  
 <213> Homo sapiens

<400> 17

gcaattttct	gcatagcatc	agcaatgagt	ctgtacaact	gtcttgctgc	actaattcat	60
aagataccat	atggacaatg	cacgattgca	tgtcgtggca	aaaacatgga	agtgagactt	120
atTTTTctct	ctggactgtg	catagcagta	gctgttggtt	gggctgtggt	tcgaaatgaa	180
gacaggtggg	cttggatttt	acaggatatc	ttggggattg	ctttctgtct	gaattttaatt	240
aaaacactga	agttgccccaa	cttcaagtca	tgtgtgatac	ttctaggcct	tctcctcctc	300
tatgatgtat	tttttggttt	cataacacca	ttcatcacaa	agaatgggtga	gagtatcatg	360
gttgaactcg	cagctggacc	ttttggaaat	aatgaaaagt	tgccagtagt	catcagagta	420
ccaaaactga	tctattttctc	agtaatgagt	gtgtgcctca	tgccctgtttc	aatattgggt	480
tttgagagaca	ttattgtacc	aggcctgttg	attgcatact	gtagaagatt	tgatgttcag	540
actggttctt	cttacatata	ctatgtttcg	tctacagttg	cctatgctat	tggcatgata	600
cttacatttg	ttgttctggg	gctgatgaaa	aaggggcaac	ctgctctcct	ctatttagta	660
ccttgcacac	ttattactgc	ctcagttggt	gcctggagac	gtaaggaaat	gaaaaagttc	720
tggaaaggta	acagctatca	gatgatggac	catttggatt	gtgcaacaaa	tgaagaaaac	780
cctgtgatat	ctggtgaaca	gattgtccag	caataatatt	atgtggaact	gctataatgt	840
gtcatttgatt	ttctacaaat	agacttcgac	tttttaaatt	gacttttgaa	ttgacaatct	900
gaaagagtct	tcaatgatat	gcttgcaaaa	atatattttt	atgagctggg	actgacagtt	960
acatcataaa	taactaaaac	gctttgcttt	taatgttaaa	gttgtgcctt	cacattaaat	1020
aaaacatatg	gtctgtgtar	tttcaaaaaa	aa			1052

<210> 18  
 <211> 1130  
 <212> DNA  
 <213> Homo sapiens

<400> 18

ggcacgaggc	catttgtata	attctttagt	aaattgtatt	aatgggagaa	tctgtaagtt	60
atgtctgaac	tttcagggtg	tcttataatt	gtctttttcc	ttatgtcaga	tggtctatgt	120
cataagaata	aaatggttca	caccaataca	agtacttagt	tgtggaaagg	gagagtagaa	180
gataaaaaatg	gagattttcc	tgtgctacag	gcttagtcaa	gcttatgggtc	tatttaatgg	240
ttatcaaagg	caattaaata	gtgttgaatg	ttctgctttt	acctacattt	catttttcat	300
gtacttagtt	acaaattgaa	ccctcttcta	tttttttcc	gtcctgtttt	ctgtttcatt	360
ttagttttcc	ttttccctga	ttatcattta	ggcatgtaag	tgacaccag	tagcattgct	420
ttaattctgc	tggtgacagt	gccaaagctt	tactatactc	tttttggtgt	ctgttgcttt	480
tctcttgcta	atttgcttga	ctagataact	aagaattcag	gtaagcatta	gctctttggt	540
cactgagaat	aatacaactt	gcaagataat	taatttggat	tggtctacat	gtatttcggt	600
tatttctctt	taccttggtc	atttattacg	acattttgaa	ttatttacat	acccatattt	660
cttctttctt	ttatggctca	gctcactatg	ctttttttta	atactggtag	cttctcctcaag	720
gttggaaaac	aagatctgaa	tactatagaa	aataataact	atttttctgt	ggtcatatta	780
aagatataat	ggctttggat	tttgggggtga	tttttctact	gtcagtttaa	aaaaaacttg	840
tctatttgca	tttgtgtgtt	attacttcta	gttaagagta	tttccaagga	aagtttcatg	900
ttacttattt	tgtttccatg	tctttttcca	aaagaactta	ttttttatat	tataataaat	960
atcagtggaa	aagtaggttt	cgttatatag	aaattaactt	taggctgggt	gcagtggctc	1020
aagcctatat	ttgggaggcc	gaggcaggag	gattgcttga	actcaggagt	tcgaaactag	1080
cgtgggcaat	gtagcgagac	ctggtctcta	caaaaaaaaaa	aaaaaaaaaa		1130

<210> 19

<211> 883  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (19)  
 <223> n equals a,t,g, or c

<400> 19  
 gtcaccgtgg gcgtttaant atgatccccg gtcagattc gcagactgca ctgaacttcg 60  
 gctctacgtt gatgaagaag aagtctgata ctgagggtcc cgcgctgctc ttccctgaga 120  
 gtgaactttc catccggata ggtagagctg ggcttctttc agacaagagt gagaatgggtg 180  
 aggcataatca gagaaagaag gcggcagcca ctggccttcc agagggtcct gctgtccctg 240  
 tgccttctcg agggaaatctg gcacagcccc gcggcagcag ctggaggagg atcgactgc 300  
 tcatcttggc catcactata cacaacgttc cagagggtct cgctgttgga gttggatttg 360  
 gggctataga aaagacggca tctgctacct ttgagagtgc caggaatttg gccattggaa 420  
 tcgggatcca gaatttcccc gagggcctgg ctgtcagcct tcccttgcca ggggcaggct 480  
 tctccacctg gagagctttc tgggtatgggc agctgagcgg catggtggag cccctggccg 540  
 gggctctttg tgccctttgcc gtggtgctgg ctgagcccat cctgccctac gctctggcct 600  
 ttgctgccgg tgccatggtc tacgtggtca tggacgacat catccccgaa gccagatca 660  
 gtggtaatgg gaaactggca tcctgggcct ccactctggg atttgtagtg atgatgtcac 720  
 tggacgttgg cctgggctag ggctgagacg ctteggaccc cgggaaaggc catacgaaga 780  
 aacagcagtg gttggcttct atgggacaac aagcttcttt cttcacatta aaactttttt 840  
 ccktctctc ttcttcaaaa aaaaaaaaaa aaaaaaactc gag 883

<210> 20  
 <211> 989  
 <212> DNA  
 <213> Homo sapiens

<400> 20  
 ctggcttggc tgctatactc ttgcccttca ctgaacctca gttttcctca tctgaatagt 60  
 tgggagactc attcctgcct ttctcatgtc cctggctatt tggtaaacca gccagtagga 120  
 agacatcgtg aaatgtatta aagtggctct agctagacag agtgggcatg ccagggtcag 180  
 cagagattct gaagtctaga ccagttccct gggtagggccg ttgtcagtcc tagcagatgg 240  
 ccaggtcagc cctcaggctg gaaatttttag ggcagctatt ggtagggtgc tcctcttgct 300  
 gtgctgagat acggtcaaga tcatacttag gcttttggtg gaagaacata caagacgaga 360  
 gaaaaaaaaa gatcatactt aggggctccc ggaatttgct ctgccctagg ttgctgagac 420  
 ctctagaacc tgtgcaggct aaaggaactc agtcggtaga tccgagagag gtggtcaggg 480  
 agaccaggag catgtctaca ctgccagcag acttttgcct cctcccccaa gccagcagga 540  
 tggcccaaaa aggtcctccc agcagatcat ctttgcagct ccttttttag ctccagtggc 600  
 agcagggatg aggaagggaag agttctatca tttttttcta atttaaaatg acatttaaaa 660  
 tactagcct agtgggggccc aggtgtggtg gctcatgcct gttgtcccag cactttggga 720  
 ggccaagacg agtggatcgc ttgagctcag gagttaaaga ccagtctggg caacatagcg 780  
 aaacgccgtc tctataaaaa aatacaaaaa ttagctggat gtggtggtgc acacctgtat 840  
 tcttagctgc ttgtggggct aaggcgaaag gatcacttga gccaggagg tcaaggctgt 900  
 agtgagctgt ttgtgccact gcactctagc ctgggtgaca aagcaaaacc ctgtctcaaa 960  
 aaaaaaaaaa aaaaaaaaaa ggccggccgc 989

<210> 21  
 <211> 495  
 <212> DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 21

ggtggaatgt	agtgaaaacg	agatgctgtc	tctwagggac	taaggaagct	atctttcctc	60
ttccgacatt	tgctgactgg	tcgatgctag	atgatcttga	gaccctgtgc	tgaggactgg	120
agaactacag	gaaaggagca	gtatctctga	attatcgtgt	ggaaggtcac	ttgtctagcc	180
cctgatgact	gtgagcctct	tcctcctgct	tgccacctct	cagtcacaag	acggctgctg	240
cgactcaggc	tcattgtccca	attcaaggca	gcaagaaggc	catggagcgg	cacctgccag	300
cagatgcccc	tgcaggccat	ctctccaggc	tcaggaacct	aaagaagaat	ctaccagat	360
gtggtgctca	cacctgtgat	cccaccactt	tgggaggctg	aggcaagagg	atcacttgag	420
cccaggagtt	ggagaccaac	gtaggcaata	cagcaagact	cccatctcta	caaaaaaaaa	480
aaaaaaaaaac	tcgag					495

&lt;210&gt; 22

&lt;211&gt; 2317

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 22

ccctaaagag	ttgaagaact	aattgggtcgg	taaaaattgg	atattgaatt	cataagatgt	60
taaaatggac	tggatttttg	gtagtttttg	ttgcttttaa	aaaaattagt	gctagctttc	120
aagtgaatta	caaccttaaa	tttgagattt	cctttgggtga	accatggaag	tttaccaggt	180
ggtaaggaga	actgtaattg	ttaggattct	gaataagtac	tgtgttttaa	tcacagctct	240
taattcaaag	cattgattta	attccacgta	gtctgttata	ttcagaaaca	taaaaacaag	300
tggaaaaagt	atgaccccgag	tgtcggagat	ggctatgtgt	gcatgtatat	acaaatagac	360
acgtatatgt	gcatgttacc	tttacgtaca	tgtggaaaaa	cagtttcta	taagtcaata	420
tgtgtcttgt	atthtgcata	attagagtat	gatttttcta	atggctcgagg	gccttttttg	480
tgggccgcag	tttggattta	tgtgggtatgt	tgatgaagac	ttagtgaata	gccacagtac	540
tcagcttttc	ctctcacaga	ttaatctgcc	agtttctccc	actgtgtatt	gtgtatatgt	600
gatagaattt	gaggggggaaa	ataacacacc	agctaattgat	gaaacgaact	ggctctagtc	660
tgtaaaggtaa	cgggaccagc	ccaattatat	aactgattga	ggcattgcc	tttttcactt	720
aactctttga	atcaagtc	aattttat	aataattttt	ttgaggcaga	gtttcgtct	780
tgtcgcctcag	gctggagtgc	agtggcccaa	tcttggtcca	ctgcaacctc	cgctcccag	840
gttcaagggga	ttctcctgcc	tcagcctcct	gagtggctgg	gattacaggc	accggccacc	900
aagcctagct	atthtttttg	tatttttttag	tagagacggg	gtttcaccat	gttggccggg	960
ctggtctaca	actcctgact	tcaggtgatt	caccggcctc	ggcctccac	acagctggga	1020
ttacaggtgt	gagccaccgt	gcccgaacctg	aatcaagata	ttatttaaaa	gaactgtttg	1080
atgttattta	tttattcatg	tcttcaatag	gtattttacat	gtctgtcttc	ggagatgggtg	1140
ttagagggtt	tttttttttt	ttttgagacc	gagtccttgc	ctgttgccca	ggctggagg	1200
cagtggcgcg	atctcggctc	actgcaagct	ccgcctcccg	aattcacgcc	attctcctgc	1260
ctcagcctcc	tgagtggctg	ggactacagg	cgcccgcac	cacgcccggc	taatatthttg	1320
catttttttagt	ataggtgggg	tttcaccgtg	ttagccagga	tgggtgtcgat	ctcctgacct	1380
cgtgattcgc	ccgcttcggc	ttcctaaagt	gctgggatta	caggcgtgag	ccaccaagcc	1440
cggccggtga	tagagtthttg	aacaagacaa	agctccttgc	aaagctaacc	ttgggagggtt	1500
tggggaaaac	cacaaagagg	gtgacaagat	aatttcagat	agggttaagg	gataggaaga	1560
aaatgaagat	gggacatgtt	aagtaataat	aatagatgac	atthgaacac	tgtgccagtc	1620
actctgtcga	ttgtthttaca	tataccttgt	gacaacccta	agaggtaggc	accgttatta	1680
cggacatttt	acaggtgaaa	cagggacaca	ggaaaagtaa	gtaacatgcc	cagctgttga	1740
atcaaggcag	cccgggacca	gagtcactc	tctgagaaat	ggcatttggg	caggatcgag	1800
aatgaggagg	agatccagtg	tggcagaggc	cctggggagg	aatgggctgg	aagtattcga	1860
gaaacccaaa	agtaagagt	gcctgagtgg	cccagagagg	ttgatgggag	gcaggagtca	1920
gagcgtgtct	accctcgtag	gccattggag	gcttacatgt	ggaagggaca	ggthtctgatt	1980
cctgtthtaa	aagagggtctg	ctgtccgggc	gcgggtggctc	acgcctgtag	tcccagcact	2040
ttgggaggcc	gaggcggg	gatcgcgagg	tcgggagatc	gagaccatcc	tggctaacac	2100

cccgtctcta	ctaaaaatac	aaaaacaaaa	ttagcccggc	atgggtggcgg	gcgcctgtgg	2160
tctcagctgc	tcgggaggct	gaggcgaaag	aatggcgtga	acctggaagg	cggagcttgc	2220
agtgagccgg	gattgtgcca	ctgcactcca	gcttgggcga	cagagcgaga	ctccatctcc	2280
aaaaaggaat	tcgatatcaa	gcttatcgat	accgtcgc			2317

&lt;210&gt; 23

&lt;211&gt; 1726

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 23

ctttttggct	ctcattttga	atttttcaag	agctcatgtt	ctttgtcttc	attaaaaaaa	60
aaaagttctt	atatcgtgta	tgaatgtcat	tcgggatata	tatacatata	tgcacatacc	120
tcatttttat	tgcatttcac	tttattgcac	tttgcaaagt	gacatttttt	acagattcaa	180
ggtttggcaa	ccctatgtcc	ataagtctgt	cagcaccatt	tttetaacat	atgtgctcat	240
tttgccctct	tgtcacattt	tttttttttc	ctgagacagg	gtcttgcctc	gtcaccagg	300
ctggaatgca	gtgggtgta	tatgcctcac	tgccggcctg	acctcttggg	ctcaagggat	360
cctcttgcct	gcgcttcttg	agtagctgag	actacagatg	tacaccacca	cacaccagc	420
taagttttta	atttttttat	agagatgggg	tttccctatg	ttgcccgaag	tgctctcgaa	480
ctcctgggct	taagtgatcc	tcccacctca	gcctttcaaa	gtgctgggat	tacaggcatg	540
agccacagca	cctggtctct	gtgtcacgtt	ataataattc	tgccaatatt	ccagatttcg	600
tcattattaa	atctgttatg	gtgatctgtg	atcagcgaa	tctgatgtta	ctgtctaatt	660
gctttgggat	gcagtgaacc	cgtcagagtc	atccatgagg	gttggaatca	acttcttcca	720
aaatcctgtt	aatcaagagt	gaacttaatc	gattaatgtt	gtgtatgttc	tgactgctcc	780
accaatctgt	gggtccccta	tcactctccc	tctcctcagg	cctccctatt	ccctgagaca	840
caataatatt	gaaattagac	caattaataa	ccctgcaatg	tgaaaggaag	aagttacatg	900
tctctcactt	taaatcaaaa	gctagaaatt	attaagctta	gtgaggaggg	catttcgaaa	960
gctgagagag	gctgaaagct	aggccgggtg	tgccaaatag	ctagccaagt	tgtgaatgca	1020
taggaaaagt	tcttgaagga	aattaaaatt	gttactccag	tgaacacaca	aatgttaagt	1080
aagcaaaa	gccttattgc	ttatggaaag	aaagtctgaa	tggctctgaat	agaagatcac	1140
atcagccaaa	acatgtcctt	aagccaaagc	ctaacttata	atagatcagg	ccctaagtct	1200
cttccattcc	ttgaaggcac	agagagggtg	agaagttgca	gaagaaaagt	tggaagctag	1260
ccaaccttgg	tttgtgcagt	ttaaggaaaa	aagccatctc	cataacatgg	aagtgcagaa	1320
tgaagcagca	ggcactagt	gggaagctgc	agcaagttat	acagaaaatc	tagctaata	1380
tgagggtggc	tacactaaaa	acagattttc	aatggagaca	aaacaccctt	ctattggaag	1440
aagatgccct	ctaaagcttt	cataggtaga	gcaggtgctg	tgcatgggct	tgaagaaca	1500
ggctgattct	cttgctagag	gccaatgaag	ccagtgaatt	taagttgaag	ccagtgtctaa	1560
tttatcattc	tgaaaattgt	agggccctta	agcattatgc	taaatctact	ctgcctgtgc	1620
tctagaaatg	gaatagcaaa	gcacgaatga	cagcacatct	gtttacaaca	tgatgtgctg	1680
aatattttta	gcctatatatt	gagacctact	gctcaaaaaa	aaaaaa		1726

&lt;210&gt; 24

&lt;211&gt; 529

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 24

acgcgtccga	ttacttacgt	gctcctggct	gggatggcac	tgggcattca	gaaaagggtc	60
tccccggagg	tgctgggcct	gtgtgcaagc	acagcgtggg	tgtgggtggg	gatggagggtg	120
ctggccctgc	tcctgggcct	ctacctggcc	accgtgcgca	gtgacctgag	cacctttcac	180
ctgctggcct	acagtggcta	caaatacgtg	ggaatgatcc	tcagtgtgct	cacggggctg	240
ctgttcggca	gcgatggcta	ctacgtggcg	ctggcctgga	cctcatcgcc	gctcatgtac	300
ttcattgtgc	gctctttgcg	gacagcagcc	ctggggcccg	acagcatggg	gggccccgtc	360

ccccggcagc	gtctccagct	ctacctgact	ctgggagctg	cagccttcca	gccccctc	atc	420
atatactggc	tgactttcca	cctgggtccg	tgacccctg	gccccagatg	gcactgagtt		480
tttcattcat	tgaagatttg	atttccttga	aaaaaaaaa	aaaaaaaaa			529

&lt;210&gt; 25

&lt;211&gt; 1755

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 25

ggcagcagcc	tcacagcgcc	tctgctggag	ttcctgctgg	ccttgtactt	cctcttttgc		60
gatgccatgc	agctgaatga	caagtggcag	ggcttgtgct	ggcccatgat	ggacttcctg		120
cgctgtgtca	ccgcggccct	catctacttt	gctatctcca	tcacggccat	cgccaagtac		180
tcggatgggg	cttccaaagc	cgctgggggg	tctgtgcctg	acactcgggc	tgtttgtcca		240
agcagatctg	aaatggggcg	tgagctgggg	gcagcagcct	cccggggagca	gggagtcagc		300
cctgtgatgc	atcccatcca	ccctgtccac	aggtgtttgg	cttcttttgc	accatcgtgt		360
ttgcaactgr	tttctacctg	atctttaacg	acgtggccaa	attcctcaaa	caaggggact		420
ctgcagatga	gaccacagcc	cacaagacag	aagaagagaa	ttccgactcg	gactctgact		480
gaaggcctgc	gggtgccttg	gcaacctgag	ccacacaggc	ctccaccctc	gcgcctcaca		540
ggggtcgctg	gcgttggagc	ggaggcctgg	acttctgagt	tgagaggggg	gctgcggaca		600
cagcaggccc	cctacagcct	caggttctgc	ctgagcccg	cctaccaggc	ttgcccctca		660
gctcagcact	gttgaccacg	ctgcgtatga	gggcatcttg	ggtatccac	tccttctccc		720
catttctgtc	ccacaggcct	tcagcccttt	aacgtctctg	ccaaaaacca	gcacaaggag		780
acaaagcaga	gccttgtctg	tatctgggca	gcaggtgttc	catgctgcta	ggtagcgggg		840
gtcgggggtc	ttctgtttca	ctaacaggaa	caaagacaga	aaccatgaca	gggctgcccc		900
gccaggcccc	ggtaggggtt	tctgcacttg	gtgctcctgc	ccacaccagc	cactttgggtg		960
acaatgaccc	ttccaagaat	ctttgggttc	aggagacca	gttccctctt	cattcttgaa		1020
gcaggggagaa	attgaccttt	gccttgtcgc	ccagggaagt	gggctcggca	cccataacta		1080
acacctccca	cccttgga	ccatgtcttc	tgggggtgag	atgaccattc	tgggtctaag		1140
actgtttcaa	agaagagctc	atagactgac	tgggtccagaa	gacagagggg	acaacagtgg		1200
catcacagtg	acagtgtcat	ggggagctgg	gcgggcccag	ccaaaccctc	cttcttcccta		1260
gagcccagcc	agcaggcagg	agttcctgga	ccctcaggac	agtgaacttc	cagacctcag		1320
ggcaggtcta	tgggccactg	caggagatga	gaccagcctt	ctgtgttcac	ctaacgattt		1380
atactgtgta	tctgtctttg	atggaatttt	gtaacttttt	atattttttt	atgcaaaagc		1440
agcttcttaa	cagatggcat	tttctgtgac	tctaggcctc	acaaaagagc	cagagttctg		1500
gacctatgtt	tgagcattt	gtagccttat	tctcttgcgt	gtgaatctct	taccctgaaa		1560
aaaagccata	atgaattaag	ccagactgac	cacttgcttg	gagtgtgtgc	ttgaaaaaac		1620
cagagcaata	ctgttgggta	ttgtatcagg	cttcagtaca	aactggtaac	accaatgtgg		1680
atcctgacag	ctttcagttt	tagcaaaaat	acacgtgaaa	tctgactacc	atttaaaaaa		1740
aaaaaaaaaa	aaaaa						1755

&lt;210&gt; 26

&lt;211&gt; 1751

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1520)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1557)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1689)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1729)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1735)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1741)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 26

gggtgcagcc	tgatggcgca	ggaggtagac	acggcacag	gcgccgagat	gcggcggggc	60
gcgggcgcgg	ctcggggacg	cgcttcctgg	tgetgggccc	tggcgctgct	ttggctcgcg	120
gtggttccgg	gctgggtccc	ggtctcgggc	atccccctcc	ggcgccactg	gccggtgccc	180
tacaagcgct	ttgacttccg	tccaaaacct	gataccttatt	gtcaagctaa	gtatactttc	240
tgtccaactg	gctcacctat	cccagttatg	gaggggtgatg	atgacattga	agtttttcga	300
ttacaagccc	cagtatggga	atttaaatat	ggagacctcc	tgggacactt	gaaaattatg	360
catgatgcca	ttggattcag	aagtacatta	actggcaaga	actacacaat	ggaatggtat	420
gaacttttcc	aacttggcaa	ctgtacattt	ccccatctcc	gacctgaaat	ggatgcccct	480
ttctgggtgta	atcaaggcgc	tgcctgcttt	tttgagggaa	ttgatgatgt	tcactggaag	540
gaaaatggga	cattagttca	agtagcaact	atatcaggaa	acatgttcaa	ccaaatggca	600
aagtgggtga	aacaggacaa	tgaacagga	atattattatg	agacatggaa	tgtaaaagcc	660
agcccagaaa	agggggcaga	gacatggttt	gattcctacg	actgttccaa	atattgttta	720
aggaccttta	acaagttggc	tgaatttgga	gcagagttca	agaacataga	amccaactat	780
acargaatat	ttctttacag	tggagaacct	acttatctgg	gaaatgaaac	atctgttttt	840
gggccaacag	gaaacaagac	tcttggttta	gccataaaaa	gattttatta	ccccctcaaa	900
ccacatttgc	caactaaaga	atctctgttg	agtctcttgc	aaatttttga	tgcagtgatt	960
gtgcacaaac	agttctattt	gtttttataat	tttgaatatt	ggttttttacc	tatgaaattc	1020
cctttttatta	aaataacata	tgaagaaatc	cctttaccta	tcagaaacaa	aacactctct	1080
ggttttataaa	acaccttaat	tctactgctc	ttttttctcc	aatcaccagc	atctgttttt	1140
caggggggtga	ttttactttt	gtgaattcct	tagcctttct	tccttggtgc	ataaagttaa	1200
aatgcacatc	agcagaattg	ctgcatatta	acatctcagg	actcttctct	tgtaaagaag	1260
ctgaaattcg	tactatattg	gccaaagtga	gcgagttagg	tgatcttggt	ttcaatttcc	1320
gagcctttgt	taatattggag	aattatgggt	catatcagtt	atgtaggacc	tttggaacca	1380
gggtcctaca	gatagatatg	gtgtgcccag	attttaaaaa	taccttcaaa	aataaaaaat	1440
acattcagtg	acatttttcat	ggtgggagct	cttctttctg	atatggcagt	tacacttttt	1500
cacttaagtg	ctttagtttn	agactaactt	tacaacttct	ataacttttg	ggaaccnagt	1560
ttagtatagt	ctgattacat	tccattccacc	taacttttagg	cattcggttt	agacaccata	1620
actggrgkgr	atkgkgcytc	cyagratgtg	ggcaaatccc	agtggttaac	accatatttc	1680
tgggctggng	attttgggga	ctagctaggt	aaacgggctt	ggtggttcnt	ttaancatac	1740
ntaaccacca	c					1751



<210> 27  
 <211> 1212  
 <212> DNA  
 <213> Homo sapiens

<400> 27  
 gccaaagcttg gcacgargtt ggtggcgggcg tccggaggtg ctggtttgtt ctcggtgaac 60  
 ggcgcgcggg gtctctcctg agtgcgagct acgggacctt cgccatgccg gggatgggtac 120  
 tcttcggccg gcgctgggcc atcgccagcg acgacttggg cttcccaggg ttcttcgagc 180  
 tggctcgtgcg agtgctgtgg tggattggca ttctgacgtt gtatctcatg cacagaggaa 240  
 agctggactg tgctggtgga gccttgctca gcagttactt gatcgtcctc atgattctcc 300  
 tggcagttgt catatgtact gtgtcagcca tcatgtgtgt cagcatgaga ggaacgattt 360  
 gtaaccctgg accgcggaag tctatgtcta agctgcttta catccgcctg gcgctgtttt 420  
 ttccagagat ggtctggggc tctctggggg ctgcctgggt ggcagatggg gttcagtgcg 480  
 acaggacagt tgtaaacggc atcatcgcaa ccgtcgtggg cagttggatc atcatcgctg 540  
 ccacagtggg ttccattatc attgtctttg accctcttgg ggggaaaatg gctccatatt 600  
 cctctgccgg ccccagccac ctggatagtc atgattcaag ccagttactt aatggcctca 660  
 agacagcagc tacaagcgtg tgggaaacca gaatcaagct cttgtgctgt tgcattggga 720  
 aagacgacca tactcgggtt gcttyttcga gtacggcaga gctttttctca acctactttt 780  
 cagacacaga tctggtgccc agcgacattg cggcgggcct cgccctgctt catcagcaac 840  
 aggacaatat caggaacaac caagacctgc ccaggtgggtc tgccatgccc cagggagctc 900  
 ccaggaagct gatctggatg cagaattaga aaactgccat cattacatgc agtttgagc 960  
 agcggcctat ggggtgsgccc tctacatcta cagaaacccc ctacggggc tgtgcaggay 1020  
 tgggtggtgac tgaaattagc tggacatggg tgcacacacc tgtaatcaca gctactcggg 1080  
 aggttgaggc gggagaatcg cttgaaccag ggagttggag gttgcagtga gtggagatca 1140  
 caccattgcc ctgcagccta agcaacagag caagattctg tctcaaaaaa aaaaaaaaaa 1200  
 aaaaaactcg ag 1212

<210> 28  
 <211> 1112  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1105)  
 <223> n equals a,t,g, or c

<400> 28  
 ggcacgagca aacatccagg agtgtgcacc ggtcatgcaa ggtgttttgt ttggctttgt 60  
 ctggcttttt agttttttgt ggcaggagaa taaatctagt gcctctccct ccacattagc 120  
 caaaagtgga agtcctgtc cagtcagcat tccttggatg cctgggtgtat tagtccgttt 180  
 ttccacactg ctataataaa aagaactgcc caagactggg taactaataa aggaaagagg 240  
 tttaattgac tcacacttct gcatgtttgg gaggcctcag gaaagttaca atcaggcaga 300  
 aggtgaagtg cgttcgtctt aatggcgcca ggtgagacag tgtgtaggat aaactgtcaa 360  
 acacttataa aaccatcata gtcacatgaga ctcattcac tgtcacgaga acagcatggg 420  
 ggaaccgccc ccatgatcta atcacctccc actaggtccc tccctccacc tgtggggatt 480  
 atgaggatta caattcaaga tgagatttgg gcaggggcac cgagccaaac catatcacct 540  
 tatatgtgcc cagtgttgac ctaggcgctg ggatgcagaa acaaacacga catgggctgt 600  
 gccttgggga gctcacactc ttgctggaga agcatgctga ttcctaaata agaaatgcta 660  
 tgtgctgtgt acagagtacc atggaaggca ggatgaactc tttgggagga agaagcaagg 720  
 aaagctttag agagttgctg gcttttgagg gatggagcag gcattttcta catggggaaa 780  
 gtgtagggaaa gagtattcca ggcagagtgg agagcaagag caaaggcggg gaagcctgtg 840

ctgcgaattc	cttgccgggc	aggatccctg	tcttactgct	gttttagagat	caatatatgt	900
caagtgactg	gaagtgtggt	ttttgttctg	ggactagtag	gtagaacaga	aagagttggg	960
atggagtgag	caacccatgg	agaaatagag	gctcggggtc	agctgataca	aggcgttgta	1020
taccaagctg	aggagcacia	gattttggaac	ataataccaa	atgctgggga	gccatgggag	1080
ggccatggga	gctctgatag	tgttntctcg	ag			1112

&lt;210&gt; 29

&lt;211&gt; 748

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 29

ggcagcagcg	aaactgtttt	ccaatgtggc	tgaaccactc	tgcatttcca	ccagtaatga	60
gaatgagagt	tgctgttgct	ccacggcctc	accagcattt	ggtggtgtca	gtgtccttga	120
tttttagccat	cctaataagt	gttagtggct	atcattgttt	tcattttgcaa	ttctcttaca	180
tggtgtkgaa	catctttccc	catgtttatt	tgatcatctgc	atatcttctt	cggccagtta	240
tctgttcaga	tctttttgcc	gtttttgttt	gcttgcattg	ttgttttgtgt	ttgatttttt	300
aaagaaagct	ttttttatta	ttgagttgta	atagtgtctg	tatagtgtgg	ataacagttc	360
tctatcagat	aggtcttttg	caaataattt	ccccaatctg	tggactgtct	tctcattctt	420
ttgataaatg	gcttttaaaat	aataatctgg	ccgggcgcag	tggctcatgc	ctgtaattcc	480
agcacttttg	gaggccaagg	gcagatcatc	tgaggtcggg	agttcgagac	cagcctgacc	540
aacatggaga	aaccccatct	ctactaaaaa	tataaaatta	gtcgggcgtg	gaggcacatg	600
cctgtaatcc	cagctacttg	agaggctgag	acaggagaat	ctcttgaacc	cgggaggtgg	660
aggttgcaat	gagccgaaat	cgtgccactg	tattccagcc	tggacaataa	gagcaaaact	720
ccatctcaaa	aaaaaaaaaa	aactcgag				748

&lt;210&gt; 30

&lt;211&gt; 778

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

ggaactaaaa	agcttttgtgt	tcttcagggt	gggtggcagg	gggatatagt	gaggggtggac	60
caggggagaat	gaccataggg	cactaagtaa	ggctgggatt	ggatcagcag	aaatccaacc	120
ctctaaccctt	agggtaggga	gtgctaagga	tctggggaaa	ccatgggctg	ggaagctgct	180
cttgctctcc	tcgtgtctgc	tgtttttttc	ccttgggtgta	ctatacagag	gccagatggt	240
ggcaccacct	ctccaggagg	attggaaagg	aggagtaaag	gattctgatt	tgattgatga	300
ttccagtga	tccccaatcc	caccatctta	cctgggaatat	aaggctgcct	tgtaccctt	360
ttctgagcac	aagtctgtgc	gtaatgcaac	tgactctctt	acttttttct	tagtaactga	420
tcatttccta	gacaaccaag	attctcaata	agtcccagtc	tcatacaaaa	tattaatatt	480
tccttttctt	cataccaact	tgactatggt	tactgaaac	ccacaggtct	tgggacagaa	540
tgaggcatta	cctcattgaa	ctttagctgc	ctgcatgagt	cctctgtcct	caagtctttc	600
tcagatcatt	tctcaagctg	gctcccagct	tagggcaaaag	agaatctcca	tgatgtgctg	660
acttctagct	tgccacagac	acaattctac	tccaaagtca	gcctggcata	gtaacattga	720
tgtcagggga	gacatatcag	tttgaggcca	tacaaaaaaa	aaaaaaaaaa	aactcgag	778

&lt;210&gt; 31

&lt;211&gt; 1324

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

acgagcta	at	gattctt	gct	gaagatgg	gcc	agagtaat	ca	gagtaatta	aa	tttgggga	aat	60
ggtgaagg	at	aaggaac	ctg	atcagata	tac	aagggtgg	ggg	gtactctt	gc	taaactga	act	120
cagtaggg	tc	cttgctaa	aaa	ctggtttt	ta	caagagag	ag	cacaggtag	g	tctacaag	aa	180
gattcggg	ag	actgact	aaa	gtttcat	caa	gaatcttt	gt	caggagac	at	gaccttt	atg	240
atacttaa	gt	ttttcttt	ttt	atgcggtt	ttt	gttttaa	aca	ggctaata	gc	tcgtcag	ctt	300
gctaaaat	cc	atgctatt	tca	tgcacaca	aat	ggctggat	cc	ccaaatct	aa	tctttgg	cta	360
aagatggg	aa	agtatttt	ctc	tctcatt	ccc	acaggatt	tg	cagatga	aga	cattaata	aaa	420
aggtaaa	att	atttttac	at	ttgaaatt	at	gttttac	att	gctttg	ctct	atgatagg	gt	480
ttcaaagg	ta	attgtaa	agt	ttcattgt	at	aaaatct	ggg	tttcttt	ctt	tgcattga	ag	540
taaagtaa	gc	attgatt	ctt	tggctgt	cag	atagcact	ac	agaaata	act	gcctctcc	at	600
ccccctc	agt	gtcccc	ctcc	aaaaaat	atg	ccctaca	aca	gcaagggg	ca	gaagtgg	aag	660
taggggaa	aca	ccacttaa	aaa	ataaaga	ggg	aggtggta	aat	ggtgaag	caa	ggattttt	ctt	720
tgactttt	ta	agatact	gca	gggttgag	ag	gcaagtct	tag	tattatat	ag	aataagag	ca	780
caagagcc	tg	gagccaa	act	gagattaa	aat	cttagtcc	tg	ctagttaa	aca	tttctgtt	gt	840
gtaactca	tt	caactagg	gga	acttaac	cta	actgttt	cc	tatctata	aaa	atggaaat	ta	900
cagtagtag	t	atattaac	cca	tatagag	ttt	ttgtgagg	at	tgagatag	ta	tatgtaa	agt	960
tctttaaa	ac	agtgcct	ggt	catcact	tta	gtgttgag	gg	agctgct	gtt	ttaaaaat	ta	1020
ctattgtt	at	tcaaaga	aagg	ttatttg	agt	tatat	ttttt	ccctagg	ctc	tccaagg	tat	1080
actttaa	atc	cttgagg	tta	atgattc	ttt	ggaaaag	ctg	gaggtgt	gct	gtggtaa	ata	1140
ataggaag	aa	aaccctt	gcc	ccaataga	aaa	ataataca	aac	tagaacata	aa	aacacaat	ta	1200
aaatatta	aaa	tacatttt	gt	atttcttt	ta	ttccattt	tg	tttgttc	atg	atttaagt	ttt	1260
tataatcc	tt	cgaatccc	ac	aattttc	catt	cgacact	acc	tttaaaaa	aa	aaaaaaaa		1320
aaaa												1324

&lt;210&gt; 32

&lt;211&gt; 739

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (732)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 32

ggcacgag	ga	caggatc	ctg	gtttggg	tac	cttagt	ttta	tagaaac	cca	ggtggaa	acc	60
tagattgc	ag	ggcattt	gtt	tgagact	att	tagccac	agc	agggcaa	agca	ggaagat	gca	120
gcctgtc	act	gctaact	cct	tagtatta	aaa	actgtca	aac	atgggag	gta	actgctg	atg	180
catttttc	cag	ttgatag	ttt	atatact	ttt	tctgaag	gat	cctaata	gata	gttaacc	att	240
tctcatt	ttt	attttg	ctgg	attgttt	ttc	gtttttt	gct	tcagcatt	ct	tgctttt	gct	300
gtgctt	act	ttggag	ttt	gattcc	ctgt	gtcact	gtt	tctttc	gcat	acacct	ctca	360
ggtttac	aca	gtaaaca	atg	tgaatgt	gat	cacaaaa	ata	cgcacaga	aac	atctgac	cga	420
ggaggaaa	aaa	aagagata	tata	aaggta	atca	ccaccacc	ct	cccacct	cct	gtttt	gtt	480
tatttttt	taa	gcctagag	ggg	aactct	ttgt	tggctct	gtt	aagt	ttagg	g	g	540
tgggtt	gtg	taagccta	ac	cctaact	ctc	wctctct	ctc	tctct	ttttt	ttt	ttt	600
aggcaa	agt	tcgccct	gtc	acccagg	ctg	gagtgc	agt	gcacgac	ctt	ggctc	act	660
aacctct	gcc	tcctgag	gca	ggagaat	cac	ttgaac	ctgg	caggcgg	gag	ttttg	gtg	720
ctgagg	tc	gncatt	gca									739

&lt;210&gt; 33

&lt;211&gt; 1462

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 33

ggccatcggc	ggggcagtcg	cgggatgcgc	ccgggagcca	cagcctgagc	tttagcccat	60
gaggaggatg	tgaccgggac	tgagtcagga	gccctctgga	agcatggaga	ctgtggtgat	120
tgttgccata	ggtgtgctgg	ccaccatctt	tctggcttcg	tttgagcct	tggtgctggt	180
ttgcaggcag	cgctactgcc	ggccgcgaga	cctgctgcag	cgctatgatt	ctaagcccat	240
tgtggacctc	attggtgcca	tggagaccca	gtctgagccc	tctgagttag	aactggacga	300
tgctcgttatc	accaaccccc	acattgagggc	cattctggag	aatgaagact	ggatcgaaga	360
tgccctcgggt	ctcatgtccc	actgcattgc	catcttgaag	atttgtcaca	ctctgacaga	420
gaagcttggt	gccatgacaa	tgggctctgg	ggccaagatg	aagacttcag	ccagtgtcag	480
cgacatcatt	gtggtggcca	agcggatcag	ccccaggggtg	gatgatgttg	tgaagtcgat	540
gtaccctccg	ttggacccca	aactcctgga	cgcacggacg	actgccctgc	tcctgtctgt	600
cagtcacctg	gtgctggtga	caaggaatgc	ctgccatctg	acgggaggcc	tggactggat	660
tgaccagtct	ctgtcggctg	ctgaggagca	tttggagtc	cttcgagaag	cagccctagc	720
ttctgagcca	gataaaggcc	tcccaggccc	tgaaggcttc	ctgcaggagc	agtctgcaat	780
ttagtgccta	caggccagca	gctagccatg	aaggccccctg	ccgccatccc	tggatggctc	840
agcttagcct	tctacttttt	cctatagagt	tagttgttct	ccayggctgg	agagttcagc	900
tgtgtgtgca	tagtaaagca	ggagatcccc	gtcagtttat	gcctcttttg	cagttgcaaa	960
ctgtggctgg	tgagtggcag	tctaatacta	cagttagggg	agatgccatt	cactctctgc	1020
aagaggagta	ttgaaaactg	gtggactgtc	agctttatct	agctcaccta	gtgttttcaa	1080
gaaaattgag	ccaccgtcta	agaaatcaag	aggtttcaca	ttaaaattag	aatttctggc	1140
ctctctcgat	cggtcagaat	gtgtggcaat	tctgatctgc	attttcagaa	gaggacaatc	1200
aattgaaact	aagtaggggt	ttcttctttt	ggcaagactt	gtactctctc	acctggcctg	1260
tttcttttat	ttgtattatc	tgccctggctc	ctgaggcgctc	tgggtctctc	ctctcccttg	1320
caggtttggg	tttgaagctg	aggaactaca	aagttgatga	tttctttttt	atctttatgc	1380
ctgcaatttt	acctagctac	cactaggtgg	atagtaaatt	tatacttatg	tttccctcaa	1440
aaaaaaaaaa	aaaaaactcg	ag				1462

&lt;210&gt; 34

&lt;211&gt; 2815

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 34

gggtcctgga	gtgccctcgg	ctgatagaga	ctatagttcg	agagttcttg	cccaccagtt	60
ggtctcctgt	gggggcaggg	cctacccta	gtctatacaa	agtaccctgt	gctactgcca	120
tgaactact	tcgtgtcctg	gcctcagctg	ggaggaatat	tgctgcccgg	ctgttgagca	180
gctttgatct	cgggagccgc	ctgtgccgca	tcatagctga	ggctcccaa	gaactggcct	240
tgccccaga	ggaagctgag	atgctgagca	ccgaggccct	ccgtctgtgg	gctgtggctg	300
cctcctatgg	ccagggcggg	tacctttaca	gggagctcta	cccagtgtctg	atgcgggcct	360
tgaggtgggt	gccgcgggag	ctcagcacc	acccacctca	accctgtcc	atgcagcgga	420
tagcctcact	gctcactctc	ctcaccagc	taaccctggc	agccggcag	accctgtctg	480
aaaccatcag	tgattctgct	gaggccagcc	tctcgccac	cccttctta	gtcacttgga	540
cacaggtgtc	tgggctccag	cctcttggtg	agccgtgtct	aaggcagacc	ttgaagttgc	600
tgtccagacc	tgagatgtgg	agagccgtgg	gcccagtgcc	cggtgcctgc	ctgttggtcc	660
tgggagccta	ctaccaggcc	tggagccagc	aaccaagctc	atgcccgag	gattggctcc	720
aggacatgga	gcgcctgtca	gagagctgct	gctgccactg	ctgagtcagc	ccacactggg	780
cagcctgtgg	gattccctta	ggcactgtct	ccttctctgc	aaccgctgt	cctgtgtgcc	840
agcccttgaa	gctccccca	gcctcgtgtc	actgggctgc	tgggaggct	gccccgtct	900
cagtctggct	ggctcagcct	cacccttccc	attcctcact	gccctcctct	ctcttcttaa	960
taccctggcc	cagatccaca	aggggctgtg	tggccagctg	gctgccatat	tggctgcccc	1020
gggactccag	aattacttcc	tccagtgtgt	ggctcctggg	gctgccccac	acctcacacc	1080
tttctctgca	tgggcccctgc	gccatgagta	ccacctgcag	tacctggcac	tcgctctggc	1140
ccagaaagcg	gcagcgctgc	agccactgcc	agccacctat	gctgccctct	atcatgggtat	1200

ggccttgccc	ctgctgagcc	ggctgctgcc	cggaagttag	tacctacccc	atgagctgct	1260
gctgagctgt	gtattccggc	tggagttcct	cccggaaaga	acatcagggg	gtccagaggg	1320
agccgacttc	tctgaccagc	tgtcgttagg	aagcagcaga	gtccctcggg	gtgggcaagg	1380
gactctgctg	gctcaggcct	gccaggacct	ccccagcatc	cgcaactgct	acctgactca	1440
ttgctcgcca	gcccagagcca	gtctgctggc	ctcccagggt	ctgcaccgag	gggagctaca	1500
gcgagtccca	accctgctac	tgcccattgcc	tacggagccg	ctgctgcccc	ccgactggcc	1560
cttctctcac	tgattcgctt	ctacaccggg	cttcagacac	ccccctcgga	ctctctccac	1620
agacaccatg	ggcacagcca	tgcgggtcct	gcagtgggtg	ctagttttgg	agagctggcg	1680
cccccaggct	ctctgggctg	tgccccctgc	tgccgcctg	gcacggctca	tgtgtgtgtt	1740
cctggtggac	agttagctgt	tccgggagtc	cccagtagag	catctgggtg	cagccctcct	1800
cgcccagctc	tgtcagcctc	aagtcttgcc	aaacctcaac	ctggactgcc	gactccctgg	1860
cctgacgtct	ttccctgacc	tctatgccaa	cttccctggat	cattttgagg	ctgtctcttt	1920
tggggaccac	ctcttttggg	ccctggtcct	cctgccccctg	cagcgtcggg	tcagtgtcac	1980
cttgccgctt	gcccctctttg	gggaacacgt	gggagccttg	cgagctctga	gcctgcctct	2040
gacccagttg	cctgtgtccc	tggagtgtta	cacagtgcct	cctgaagaca	acctggccct	2100
ccttcagctc	tacttccgga	ccctggttac	tgggtgcgtc	cgccacacgt	ggtgccccgt	2160
gctatatgct	gtggctgtgg	ctcatgtcaa	tagcttcac	ttctctcagg	acccacagag	2220
ctcagatgag	gtcaaagctg	cccgcaggag	tatgtctcag	aaaacatggc	tgtctggcaga	2280
tgaggggtctc	cggcagcacc	tcttgacta	taagcttccc	aattccacgc	tcccagaggg	2340
ctttgagctc	tattctcagt	tgccccctct	gcgtcagcac	tacctccaga	gactgacttc	2400
aacagtgtct	caaaatgggg	tatcagagac	ctaggatagt	tgatatagat	ggaaagatgg	2460
gtacgttgct	ctgtatccag	cctttcaaca	gatgtctggc	cagacgaaga	acattgtgtc	2520
ctaagtgtag	gcaggagacc	aaggagcaga	aggcttgctt	tcctggggagc	aggttgtttg	2580
agctgtttta	gagcagtgag	ccctaccatt	acatcctgat	atctggggct	tctgaaggct	2640
tgtgctggga	gtgaagagtg	gcttagctat	ttaccgcctc	tttggggaca	gggcaaacta	2700
aatgcacccc	ttcttaccta	actcccaacc	cctgcctcctg	gctgaggcat	atgaatgcta	2760
tagttgtgca	ttaaaataaa	tgttttttat	ctcctggaaa	aaaaaaaaaa	aaaaa	2815

&lt;210&gt; 35

&lt;211&gt; 1078

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 35

ggtgggctct	gtgctgggtg	ccttcctcac	cttcccaggc	ctgcggctgg	cccagaccca	60
ccgggacgca	ctgaccatgt	cggaggacag	acccatgctg	cagttcctcc	tgcacaccag	120
cttctgtctt	ccctgttcca	tctgtgggt	ctggacaaag	ccattgcac	gggacttcct	180
gcaccagccg	ccgtttgggg	agacgcgttt	ctccctgctg	tccgattctg	ccttcgactc	240
tgggcgcctc	tggttgctgg	tgggtgctgtg	cctgctgcgg	ctggcggtga	cccgggcccca	300
cctgcaggcc	tacctgtgcc	tggccaaggc	ccgggtggag	cagctgcgaa	gggaggctgg	360
ccgcacgcaa	gcccgtgaaa	tccagcagag	ggtggtccga	gtctactgct	atgtgaccgt	420
ggtgagcttg	cagtacctga	cgccgctcat	cctcaccctc	aactgcacac	ttctgctcaa	480
gacgtgagg	ggctattcct	ggggcytggg	cccagctcct	ctactatccc	cccagaccat	540
cctcagccag	cgctgcccc	atcggtctctg	gggaggacga	agtccagcag	actgcagcgc	600
ggattgccgg	ggcyctgggt	ggcctgctta	ctccccctct	cctccgtggc	gtcctggcct	660
acctcrtctg	gtggacggct	gcctgccagc	tgctcgccag	ccttttcggc	ctctacttcc	720
accagcactt	ggcaggctcc	tagctgcctg	cagaccctcc	tggggccctg	aggtctgttc	780
ctggggcagc	gggacactag	cctgccccct	ctgtttgcgc	ccccgtgtcc	ccagctgcaa	840
ggtggggccg	gactccccgg	cgttcccttc	accacagtgc	ctgaccgcgc	gcccccttg	900
gacgccagtg	ttctgcttca	gaactgtctc	tcttggggcc	agcagcatga	gggtcccag	960
gccattgtct	ccgaagcgta	tgtgccaggt	ttgagtggcr	aggggtgatgc	tggctgctct	1020
tctgaacaaa	taaaggagca	tgccgatttt	taaaaaaaaa	aaaaaaaaaa	aaaaaaaaa	1078

<210> 36  
<211> 1217  
<212> DNA  
<213> Homo sapiens

<400> 36  
cggcacgagg ttgaatgtta gccctggagg agatccatgt cttactcgct ctttctggcc 60  
cttctgtctt ttgcctctgc aattcttttt gtagctggca cgatagcagg gactgggggt 120  
ctatcctttc atggatttgc tacaatattt gtccttactg gaaaatggta acatccgggt 180  
ctgatttaat tggcattaca cttacacagg gactctgagc acccccgtca ccacaccaga 240  
cagtggacca gttttcacag ctacaaagag ctagaaatgt gtttaacatc atccagtgc 300  
tcccctaatt caaaaccatc ctactaatac aatcatattc acccataaat attacaaatg 360  
agattgattc catctcaaga caatttgtca aatacttaat tttcttcctg gatgattcta 420  
cttactggat attttagaaa gagaaatgtc tgagataaaa tccctcacat ttactcaata 480  
taacaaatta ctgtttctac tcctattctg agtagtgctt ctgaagattg tttgctgtag 540  
tggtgtcttt gataaaatga atgtcagtag tgagcctttt agagatacca tgctcagaaa 600  
tcctcttttg gatcagaaga tacctaaaat tctccccctt tgcctcactg gttagatgag 660  
tgatatattc tttggatcct gcaaagaaga gattgggttc ttttcttttc tgggtggtggt 720  
agtggttgta tctgtggctg tgatggttgt tgttacttgt ctctctctct ctctggctct 780  
ggcttttgct ttctgctag tgttctttct ctttccaaac aaatagttaa attaaacgtg 840  
agcttctgaa ttgtacttgt tcatactttc aaaacataac agattaataa aaatagatgt 900  
gtcctgattt aaaacatgcc ccctggaaag gcatgctgta ttatgaaatc atgataatat 960  
aactgcatta ttacatggca gtataaatat tagtctgttg aattcatttg tccaattgta 1020  
taactttgtg gagcagtgtt ttgaccttgc atacataatt ctggagcaag tggagtgggt 1080  
gcaggcagat gagacagtgt tatatcagga tttttcaatc aactttagtt ggaggcctgg 1140  
caattacaaa catcttcaga tgtttctgta accattataa atatgaaaaa aacctcttca 1200  
aaaaaaaaaa aaaaaaa 1217

<210> 37  
<211> 1282  
<212> DNA  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (153)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (1220)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (1222)  
<223> n equals a,t,g, or c

<220>  
<221> SITE  
<222> (1232)  
<223> n equals a,t,g, or c

<220>

<221> SITE  
 <222> (1246)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1282)  
 <223> n equals a,t,g, or c

<400> 37

actcgtgccg	aattcggcac	gagccattct	gagtttggtc	ccttcccaaa	agtaggggtt	60
ttgtgtggaa	aatctgagca	aacctctgtt	gactgttctg	gggtggagtg	aagggaagaar	120
gggctcagct	aaagaacatg	gggagattag	ggnaacaatg	ccttttattt	cttgctttta	180
aagcaatttc	aggagtttcc	tccctctttt	ggcgtcctgc	tgactccaca	gagcgggaaca	240
cccaaagctg	ggactttcca	cctctctaat	gctcagtga	gagcggggcca	gggggggtgtg	300
gaaaagaaa	ggtcctggag	gagcccaaat	tacgaatggc	tagagactgg	cattggcaag	360
cgaggaggct	tcgtcacagt	gtagtcttcc	ggttgtccga	gggtactgtc	ccaggggctg	420
gggggtrttc	cgtcttctgc	agatcaactc	ccgcaggcta	aatgtggaca	tcgcgggtatc	480
atgcttgata	aacggaccaa	taatcaagtg	gagattcatt	agaaccacat	aaccataact	540
aggttgattt	ctcaagtata	agscctggtc	tggtgcccag	setggagtgc	actgacacca	600
tcattggttca	ctgcagcctc	aaactcctga	gcccgaagtga	tycctcccac	tcagcctcac	660
aagtagctaa	gactagaggt	gtgcaccatc	amaccagct	aattttttaa	gttttttttg	720
tararatggg	gtcccactct	acaaaatatw	taagtataag	gcckgggtctg	ttgcccargc	780
tgggsaacc	ttggactaag	gcaatcctcc	agcctcagcc	tcctaaagtg	ctgggattac	840
aggcgtgagc	caccgcaccc	acctctagga	tctctactat	tgaggaaaaa	ttggaggcat	900
caaaactcaa	gggcaaaa	tgaagactcg	ctggcccacc	atggatggag	gttttctctc	960
ttaaaattcc	cacagcaccc	catggaactg	cctctcctgg	gacctcagcg	tttctctctt	1020
tgctctaagc	aatagcctct	gccactggag	attctgagat	ggccgatttc	cttttgata	1080
tttaagtttt	gaaatcatgc	tcatttggca	taggaatgtt	tcacttcagt	ctcctttaa	1140
caaaaggaca	cacaaccacg	attgcccctc	cctcccgaag	ggtcactgga	cttcatgcat	1200
cagtaatgtt	tccaaaaatn	tnttaagtac	cnacatgcag	tggcngctt	ttcatttttc	1260
caagtgaagc	catcagaaaa	an				1282

<210> 38  
 <211> 559  
 <212> DNA  
 <213> Homo sapiens

<400> 38

gattcggcac	gagctgaagc	cctgggtgcc	actgctggcc	cagcagggag	gaggttgctg	60
ctgctcgggc	tgaagtgagg	tgtgggtctg	gctgggcctc	cagtttccca	cctgggcctt	120
gattgtgagg	aaggcctggc	ctggctgcag	aagcccagaa	gcacctgagt	aggagagttc	180
ctttgtccca	cctgcagctc	attcaagcct	gtgcatgggg	gttgggggtc	tcaggatctt	240
gctttcctgt	ttaggggagg	cagcccaaaa	gagtgtctgg	accagtttgg	agagtgtctaa	300
ggaatgctgg	tctgcagcga	ccctacttgt	gctctgcgtc	ctctgccaac	tgcagcatgg	360
gtgaacatct	gtacatctgt	ccccataatg	aaaatggcct	cagcaaataa	caaaaatatt	420
accatttagc	aatcaggcac	ttattaaaag	cctggcccaa	taaacttaaa	aaaaaaaaaa	480
aaaaactcga	ggggggggcc	ggtacccaat	tcgccctata	gtgagtcgta	ttacgcgsgs	540
tcamtggccc	tcgtttaca					559

<210> 39  
 <211> 803  
 <212> DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 39

ggcagagcta	ggccaggcag	agcctagctc	ttgccagggc	agcaggaagc	cacacagtgt	60
gttgaagccg	gagcaggaga	gggggccctg	actcccatgt	gtccttgcag	gcaggagcag	120
ttcgtggact	tgtacaagga	gtttgagcca	agcctgggtc	acagcaccgt	ctacatcatg	180
gccatggcca	tccagatggc	acctttcgcc	atcaattaca	aagtaaggcc	tggggccctgc	240
cmaaâcattc	actgtctgcc	cacccagccc	caccccatga	agccatctgt	ccctcatccc	300
cacaggggccc	gcccttcctg	gagagcctgc	ccgagaacaa	gcccctgggtg	tggagtcttg	360
cagttttcact	cctggccatc	attggcctgc	tcctcgggtc	ctcgcccgac	ttcaacagcc	420
agttttggcct	cgtggacatc	cctgtggagt	tcaagctggg	cattgcccag	gtcctgctcc	480
tggactttctg	cctggcgctc	ctggccgacc	gcgtcctgca	gttcttccctg	gggacccccga	540
agctgaaagt	gccttcctga	gatggcagtg	ctggtaccca	ctgcccaccc	tggctgcccgc	600
tgggcgggaa	ccccaacagg	gccccgggag	ggaaccctgc	ccccaacccc	ccacagcaag	660
gctgtacagt	ctcgcccttg	gaagactgag	ctgggacccc	cacagccatc	cgctggcttg	720
gccagcagaa	ccagccccaa	gccagcacct	ttggtaaata	aagcagcatc	tgagatttta	780
aaaaaaaaaa	aaaaaaactc	gag				803

&lt;210&gt; 40

&lt;211&gt; 1510

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (426)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (454)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 40

cacgagaaac	attctatctt	ttatcaaagt	tgtgattcat	aacttttggg	taccaaagga	60
atctaacgaa	ataaccataa	tcataaatcc	atacagggag	actgtgtgct	tctctgtgga	120
gcctgtcaag	aagatattta	actatatgat	acatgtgaat	cgaacatca	tggatttcaa	180
actcttccct	gtgtttgtgg	caggagtgtt	tcttttcttt	tatgcaagga	ccctggagtc	240
aaagccctac	tttctattac	tcctcgggaa	ctgtgctagg	tgttctaagt	acatagtctt	300
tgtcttgctg	ttggtgaaaa	gattcatccg	aagtatagca	ccttttgggg	ctctaagtgt	360
tggttgttgg	tttgccctcag	tttatattgt	atgccagttg	atggaagatc	tgaagtggct	420
gtggtntgaa	aacaggatat	atgtatcagg	ctangtcttg	atagttggat	ttttcagctt	480
tgttgtttgt	tacaagcatg	ggccccctgc	acacgacagg	agcagaagtc	ttctgatgtg	540
gatgctgcga	ctcctctccc	tggttctggg	ctatgctggg	gtggctgtgc	ctcagtttgc	600
ctatgcagcc	ataatcctcc	tcattgtctc	ctggagtctg	cactaccac	tgagagcatg	660
cagttatatg	aggtggaaaa	tggagcagtg	gtttacatca	aaagagctgg	tgggtgaaata	720
tcttacggaa	gacgagtaca	gggagcaagc	tgatgctgaa	acgaacagtg	ctctggagga	780
gctacgccgg	gcctgccgaa	aacccgactt	tcctcatagg	ctggtcgtct	ccagactcca	840
cactcctagc	aaatttgcag	attttgttct	tggaggaagc	cacttgtcac	ctgaagaaat	900
cagtctgcat	gaagagcagt	atggccttgg	gggtgccttc	ttggaagagc	agctctttaa	960
cccagtgact	gcctgacatg	cgaccttcaa	gttgacttca	ttctggacaa	ggaagtgggc	1020
aaagggcagg	attctattaa	agttaggcag	aactgttcta	gtgaacgggtg	gcaaaaacat	1080
ttgctgtgga	gaaaaacaag	tcagtctgga	aaggaaaacc	aacccatttt	gaagataact	1140
tagcattctt	ggtgacttct	gctacttatt	gtactgtagg	tggataccaa	aattctgtga	1200



cagccactac	cacttacctt	gaatgaaggc	tttcattagg	aacaggggaa	tggcgttggt	1260
cttaaggggc	tagtaagcat	gaacaggtgc	tttgtcgaca	ccagggcact	aaatctgggc	1320
ttaatccctt	gaacctgtgt	cagaagactc	tgcaatactc	ttcctatagt	tcgtcagtat	1380
aagtccttaa	agagacctga	gacatgctgg	accagtgttt	tccaaagtac	agctcacagg	1440
ctactaccaa	gtgttggtca	ataaaggtat	tctgaggtca	actaagattg	ataaaaaaaaa	1500
aaaaaaaaaa						1510

&lt;210&gt; 41

&lt;211&gt; 1095

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 41

gcttggtggt	gctatttgct	tcttcaaatt	ctcgttatatt	aaaatatttc	tttcttgtag	60
cgttgattct	gggatcagcc	tggatgtgtc	aaacactgcc	tgccaggcct	agagctcagt	120
gcatttcttc	cctttttattc	ctgctgatgg	gattgctggc	catgaccggt	gagaggaatc	180
aaggaaccca	ttactatgag	ttctcaggat	tcattcttcaa	atctcaaagt	atgtgggtcaa	240
ttaaaccaaa	ttaaaaaaaa	gctcttggtt	aaagcaagtt	aaaaacaagc	tcttgacctt	300
gagaagaaat	gattgggtatt	aggaagactg	ttgagctgat	actgcccttc	attcattctc	360
taccctgggtg	cttggtatata	ggagcaaaagt	aagaaaataa	tcacagcttt	attgagggct	420
ctatgagcaa	ggcttggtga	ggatggaaga	gaatggagct	atcagttgat	gagaacctac	480
taggtgttga	gctccttaca	ttcattgcct	atttaaaact	ttctaacaac	ttcatgtgta	540
agcgttggtc	cgattttaaaa	aaaaaaatag	atgtggaaac	tgaacctgga	gaaggtgtgt	600
aatttggtcca	aggttgacaca	ggcaaagggg	caaaattcag	ctttaaaacc	aggactgttt	660
ccacagctcc	aagtyccctt	tattcatggg	atttgtaaga	tggagccctt	gccactgtag	720
catttataac	ttacttttga	gaataagatt	cctgaaagta	cgtttaataa	aaaaaaaaaga	780
tgtccagcta	tgtacggcag	ctcacgcctg	taatcccagc	actttgagag	gcaaaggggg	840
gaggatagct	tgaggctaag	agtttaagac	taacctgggc	aacatggcaa	gacctgtctt	900
ctaaaaaaca	aaatttagcca	gttggtggtg	catgcacctg	tagtccaagc	tactcaggag	960
gctaagggtga	gagggctcgt	tgagcccagg	agtttgaggc	tgcaagtgagc	catgatggcg	1020
ccactgcact	ccagtgcaga	gtgcaggcta	cagaatgaga	ccccatcaca	aaaaaaaaaaa	1080
aaaaaaaaaac	tcgag					1095

&lt;210&gt; 42

&lt;211&gt; 1162

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (340)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 42

ggcacgagct	gattcctaag	gaatattcta	gccaaatcat	gtatctgtgg	tttagttttt	60
ctacagtagg	gctgtgcggt	tgctgcctgc	tttatagggc	atgtggggtt	atatggtatc	120
tgctgttact	tgggcacagc	agcaccaact	cattacagga	tggaggggca	gaacgcccag	180
agcacccttg	ggctcacgtg	cggtagagct	gcaggagaga	gctgtccttt	tggtttttatg	240
tttttaatta	attctgtttc	ctcagattga	tgattaaatt	tattttttcca	gcctgaccaa	300
gaaggcgtca	ccataaccaga	tctggggagt	ctctcctcan	ctctgataga	cacagagagg	360
aatctggggc	tgcttctcgg	attacacgct	tcctatttag	caatgagcac	accgctgtct	420
cctgtcgaga	ttgaatgtgc	cagtaagaaa	atctttactt	tttgctaatt	agcagatttt	480
tttttttttg	aactgtaagt	gccattaaga	gtgggagagg	gccaggcaca	gtggttcagt	540

cctgtaatcc	cagcactttg	ggaggttggtg	gcacgtggat	tgcttgagat	caagattttg	600
agaccagcct	gggcaacatg	gcaaaacccc	atctctacaa	aaaacacaaa	aattagccag	660
gcatgttggc	acgtatttgt	agtcccagat	actcaggagg	ctgaggtagg	aggattgctt	720
gagcctggga	ggttgaggct	gcagtgagtc	atgatcatac	cactgcactc	cagcctgggt	780
gacagagcaa	gactctctct	ttaaaaaagc	aggagatggc	caggcagtgg	ctcatgcctg	840
taatcccagc	actttgggag	gctgaggcgg	gtggatcacc	tgaggtcagg	agttcaagac	900
cagcctggcc	aatgtggtga	aaccccatgt	ctactaaaaa	tgcaaaaatt	agctgggtgt	960
ggtgacgggt	gcctgtaatc	ctaggtactc	gggacgctga	cgtaggagaa	ttgcttgaac	1020
ccaggacaca	gaggttgag	tgagctgaga	tcacgccact	gcactccagc	ctgggtgaca	1080
agagcgagac	tcggtctcca	aaaaaaaaaa	aggagaggag	gattcaacac	agttgatgat	1140
gacaaaaaaa	aaaaaaaaaa	aa				1162

&lt;210&gt; 43

&lt;211&gt; 657

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (12)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 43

cccccccg	gntgcaggaa	ttcggcacar	atttttacatg	ctttttaagtt	aatgtttggaa	60
aactaatcac	aagcagtttc	taaaccacaaa	aatgacatgt	tgtaaaagga	caataaacgt	120
tgggtcaaaa	tggagcctga	gtcctggggc	ctgtgcctgc	ttcttttctc	gggaacagcc	180
ttgggctacc	caccactccc	aaggcattct	tccaaatgtg	aaatcctgga	agtaagattg	240
caccttcttc	ctctcctgat	caacatcggt	atgatgtctc	ctggtgcctc	accctttgtc	300
tgacagtatca	ctggatagga	ctggtggaaa	gggagcagcc	tgacagagct	ccaaatgtgg	360
agaatatggc	atccctccac	ctatatattga	tgtggacggt	aaggctaggc	ctgcaggatc	420
ccttatcctg	accaaagact	gtgttggggg	gccatttgaa	aatcgagagg	ttgcaaaaga	480
atacaatctt	acttgcaggt	ggatattctc	tatactctct	tttaatgcat	ctaaaaatcc	540
caaacatccc	ctggttgggt	atcacttaca	gttgtgtcca	cctttatatt	atgtactttg	600
attaaaaaaa	aaaaactttt	tgtaatatata	aaaaaaaaaa	aaaaaaaaaa	aaaaaaa	657

&lt;210&gt; 44

&lt;211&gt; 1155

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 44

ggcacgagtg	gaagtgtgag	cagaaataca	gcgagggctc	aggaaatact	agaataggca	60
acatgctctt	cctctctgct	tctatctgca	catctgcttt	atctctttgc	ctcagcagac	120
tcaccatctc	tgctcctcat	cccgcattgt	ggggaaggat	gcccacccac	acctccccag	180
gccatctgtt	agagctccaa	ccacgtggaa	tgacggaatc	cattctgttc	tctatctctg	240
ctctagtttc	aaattcctgg	ggaaaaatga	cccagctcac	ttcaggtccc	cactcttggt	300
ccagtgggct	gcaaaatttc	caagcgtagc	ttctgtcagt	tccttgcttt	gggttaggtg	360
aaaatgaagg	gaataattgt	gagctgttca	gattcaccaa	gaaattatct	actattgttg	420
ggggagaaatg	cccaggggac	agatgcattt	gggtaaggga	caataacaag	acactagaaa	480
ggaaaaatccc	aatttttatt	tcctacagag	tcagcatccc	acacattttc	cttcacagaa	540
actgacaaat	aatccatggg	ggcagcttag	cagatgggtt	gaaaaaagcg	acaggctcat	600
catcagtttt	caacaccttg	atacatcagg	cttgcccttt	gctacctcat	gcattattta	660
agcacaatgc	atctccctct	aattgtgtca	tgtgctggag	gagaatgtga	agttctgtct	720

gtcttttagca	aacatgtttc	aagtactgtc	tgtctgaaaa	ccaaatggaa	gagggtaaac	780
ttgatgatcc	acttgatttt	agtttttagga	cctggatgca	taggcagatg	tcagtttaca	840
aggattctgt	gtactttaag	gaatgttttc	tgagcatgtc	cagtacaaca	gacgctctgt	900
taggtagctg	tagttaggat	tttttggttg	taagtatgtg	aagatttaaa	tgtatcagct	960
cacttactca	gaaaatctga	ggcagtgcta	gccaaaccaa	atgggtcaag	caaatgtcat	1020
cagtatttgg	cctcttccag	tctttttact	cctctatcct	ctgtgtctgc	ttcacttcta	1080
cacaagcttt	ctctatgtgg	tggctccaga	ttttatatct	tctagtagat	atTTTTTTaa	1140
aaaaaaaaaa	aaaaa					1155

&lt;210&gt; 45

&lt;211&gt; 1112

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 45

gccggaggaa	gagcgtctgc	aaaactgggt	tcctagaagt	atagacggac	ttagcttttw	60
gtagaatttg	gtgaggagca	gcgcctcgtg	agagcagaat	ggcctggcgt	ggccagtgc	120
tcccggcagc	acgcagctct	gcggcctcca	gaattcccc	gttctgagct	tgatgccct	180
agcctgtccc	ctacctactt	cctccccctc	tctctagccc	tctcacaggg	gtgattgcta	240
cctctctgtt	ttcttgggcc	taggcaagtt	ttagaggagt	tcccaagcat	tgttatgagg	300
ccagtgtgct	cgctgggctg	ggcgggatgg	cctgggcttg	tgtgtggcct	gagggctctc	360
ctggggcctt	ctcttttccc	agtcaccttt	ggagccacag	aagcagtgca	ctcattggat	420
gtctgttctt	aacacagctt	ctctttctac	attaaaaaaa	atcattattg	cattttggaa	480
agcagtgtct	atcaaaaagca	acttttataa	cctattttat	tgttccttta	aatgttctct	540
cccgtgaaa	ctgccctgga	gaggctatct	gctgctcttc	catttaccca	catcaggtta	600
ttctccatgt	cactcagtg	agatgactcc	agatgtgttt	aaagmctgga	caattcacct	660
atactgtgta	ggaaattacc	tccttaatta	cctgggtmgaa	ttgtcagcag	acatgttcat	720
ccgatgatag	tactgcagtt	ttctattaat	aatttgcaga	cttttatcta	acctgcactc	780
atgtacagat	tattaaaagt	tttaaaatgt	aactgatcag	tattgatcaa	tcattgtctt	840
gatttttttt	tacagcgtat	atttctaate	atatttttta	aagccaagag	aactggttga	900
atgaatgttt	attttcctga	aggtattttt	aagataaagc	ttcctaattg	cgtgtaaact	960
ttgcataatg	atgtagtttg	atacatattg	tcacatttga	aaatcttgtg	ggttgtaact	1020
ggttttatac	aaaatatcga	atagtggaaa	ttgtataatt	acaatcatgt	aattaaaagt	1080
attaacccaa	aaaaaaaaaa	aaaaaaytcg	ag			1112

&lt;210&gt; 46

&lt;211&gt; 4023

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1049)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (2758)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 46

cccacgcgtc	cgtccaaaca	tcaggaggca	ggcagcatgg	taaatgagaa	agaagccagg	60
actgggagtc	caaagtcctg	gcttctatgt	ctggctttgc	tactaatcaa	atatgtgact	120

ttttgcaaac	catacctcac	taaacccttac	tttcttcatt	tgagcgtgtt	ggaccagctg	180
tcccaggaa	cccccttga	ttgatctgag	aaggcaagga	taagtttttc	aaaggaaaga	240
aagaggagta	gtcagtcgc	agtacagtag	acacaagccc	caggacatct	gagtgtcttt	300
cagcaagaac	tctctgtgat	atttcaactac	aatttctctg	gcacctggg	actctcctca	360
gcccttgtgg	tggtgggtct	tgtttaacta	gcagttccct	ccattctatg	cctgtgaaga	420
atctatcacc	taccatgtga	ttacagtgc	gatttttttt	tccttttctt	tttctttttc	480
tttctttttt	tttttttttt	tgtttgagac	ggagtctcgc	tttgtcacc	aggctgcagc	540
gcagtggcgc	gatctcggct	cactgcaagc	tccgcctccc	gggttcaccg	ccattctcct	600
gcctcagcct	cccgagtagc	tgggactata	ggcgcccgcc	accgtgcctg	gctaattttt	660
tctattttta	gtagagacag	ggtttcaccg	tgtagccag	gatggctctc	atctcctgac	720
gtggtgatcc	gcccgcctcg	ggctcccaaa	gtgctgggat	tacgggcgtg	agccactgcg	780
cccgccctac	agtgcggata	ttttatgaga	gaggagatca	caactcagtc	cccaagccct	840
caacccttaa	tacatactat	cgtatgaaat	gcctctttcc	aaattcagcc	ttttctaaaa	900
ctcaagatga	gaaaactgct	gatgaggctc	actttctaaa	ataccggaat	ttgcaatata	960
gggagaatag	tttttcatgt	ttctttgttt	aagcaataga	aagaaaggaa	acttatgtcg	1020
tttacttttc	aggccataga	ggttttcana	acaacttgaa	aacatgatca	aattagccaa	1080
acttctgata	gtttttcaatg	tagtctgtga	tcattgggata	atttagcctc	agttcttttt	1140
ctgaaattgt	gtttttgaatg	tttgatttga	cttattttacc	atcaaacttg	ctataagggt	1200
attactctaa	tgaataagca	tattccctta	attgggacaa	tttactatta	tttctttcat	1260
aaagtagggc	accattcacc	atctatttcc	tggtctctta	gttatcaaaa	tgtaaagctc	1320
attgctattc	atcccggcac	agcaattata	tgagaggcat	gaagctggct	gaattctgca	1380
tcattaggaa	tgacacagcc	tcatacatt	gacaccagtg	cttgtctctc	acaccaatcc	1440
aaattaagac	caactgaaaa	tagtcagagt	ttcctctgga	gctccttttt	gaagagacat	1500
atgtttttta	gtctggtggt	acccaaaatt	gaacaaaaaa	tgggtgctgc	ttctcttaat	1560
aggcaaaact	atgctgcagg	ataatgtatt	catgcagggt	cttcagcca	gaccccaa	1620
catccctccc	ttcactagaa	tttttctgtt	taattcgatg	gccactctcc	acagggatcc	1680
attctgtgtc	ttattacagg	agatgctcaa	tgaatgaggg	acttatcttc	tagaaatgca	1740
gctccgaggt	agtctgttga	gtgaaataat	gaatccatta	tcacaaaata	aattgaaagc	1800
tgtctgacat	ttggacaatt	tttattttgt	ttcacattgt	tctgaaaact	atactgtttc	1860
ttttctccct	attattttaa	taagcaaatg	atgaacagat	tacaaaattg	aggacactcg	1920
aggtagggaa	ggagcccctc	gacaggagga	tcaggacata	gtaccaaggg	caagagaaac	1980
gattcaataa	acactattta	ctatatattt	taggcatggt	tctaggtaat	cacatgataa	2040
gtagttgaaa	gaactgaaaa	tgttttatct	gcaagaaaag	ggcaagtgtg	atatcttcaa	2100
atttttagaaa	gaatgtaaat	tagaatttga	cttaatttgg	tgtagttctt	gtgggcagaa	2160
attgaattga	ataggctgaa	agttataaga	aggattttag	ctcagtattg	atactggatt	2220
gctcatgggt	ggtgagagtt	actcatcact	ggaagagttc	aagcaggggc	cataagaaat	2280
ctcagggatt	ttataagggtg	attcatgctc	tgggaaaagg	atgccttggg	ttattgtgtc	2340
agggtacttc	taactctagg	attctgggtt	ctaagatctg	gactctagtc	ttgccactca	2400
cctgccatca	agaacatggt	cctcatctgc	aggacaggac	caagatggct	ctgtctacct	2460
taccgggttg	ctgtgaggcg	tgattgtgat	aaaatacata	aaggcagttt	ttaagctctg	2520
aagcactagt	taaatgtgta	gcgtatttta	agattctggt	gtatgtacaa	ttgttttagca	2580
gtctctctct	ctttctttct	ctttctttta	tcagagatag	atgattttcc	ctcttatttc	2640
caccagtttg	gcttttcagg	gaagggtggc	gctggcagaa	tcccctgaca	acaaaaggta	2700
cagcaaaaaa	gtggaggcct	aaagaaaaca	tgtgctagct	cttttagcccc	tgaatagnta	2760
agtcacatgt	cagcctgtct	tccttcatct	gtttgggagg	aggcagatta	gagtcacact	2820
gtcatcatgc	tctttccctc	cagaagcagc	tgtaaggttt	ttggtagctg	tcagtgtctg	2880
caaacagtgc	ttttctcaca	gaactactgg	aaagagtcct	ggctcggaaa	acttgctctt	2940
gaaagtggca	cggccagagc	aggggtctct	agagggtcgt	gccacctcta	cctgccacag	3000
gttcatttgt	cggtcaggta	agtttagaggc	agcagttccc	cacctgccct	ctggataaca	3060
gcagcctggg	gtgtctcctg	agtcattgtt	ccacttctgt	cttacaggcc	tcattttcct	3120
acctatcttt	ctgtaaaaat	gaaagtcagg	agtcttatga	aacttaccat	tattcaatac	3180
aggcttttgg	tttttttctt	taaattagat	agggttaggt	aagaagtaga	gttctataga	3240
acgttcatag	gaagcaacaa	aagttgatct	cttggtctct	acaataggag	aggattgggc	3300
tagatacctt	caaagctgac	ttgcccta	attctagtat	gaaatgatc	gaaggtagac	3360
ctgcccctat	catgtcaggc	agtgagtaca	gttaaaacat	tgggaattgg	taaaggaaag	3420

aaaaaaactg	aaaagaaccc	tttgaagtta	gacaaactgt	ccagagacat	agtgcataaaa	3480
tcctccytct	ttttcttycc	acagcttcta	gaattcctct	ccagagctac	tctcaagtta	3540
tatccagggg	acaggcccct	ttggctccaa	cccacacgcc	tgaactttaa	ggatcattgg	3600
actatcttct	ctgtggccar	cgcagctctc	ttctgtgttc	acagaatggc	catgataggc	3660
atgtcttttt	cccaccact	ggaaggctca	caggcaagg	gagagaggac	acagaagggtg	3720
ccaacactgt	cgctacagta	aggacctgaa	gtgactttga	gaaattcacc	ctcacaacc	3780
ttccttcagg	agcaggcatt	ggtagtgcag	aggcacagat	tccgtccttt	accagctgca	3840
gaatcttggg	caagttacat	agcctctgtg	agcctcatcg	gtaaacagtg	ggggttatga	3900
aaccacctc	acagggttgt	tgtgaggatc	caatgagttg	athtaggtaa	gcacctagca	3960
catgccgtgg	caccaagtaa	gcactcaata	aatcactcaa	ctccttttaa	aaaaaaaaaa	4020
aaa						4023

&lt;210&gt; 47

&lt;211&gt; 542

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (389)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 47

agggcacgag	tttttttatg	actacataat	gtttattgcg	atctatttta	aggcttttca	60
tggatctttt	cagctatgca	catggttagt	cataatgatt	gtcatttttag	gtcagagtgt	120
ctcagcctta	gcattgttga	cattttgggt	aattctttgt	tgtaggggct	gtcctgtaca	180
ctgtaggggtg	tttagcagca	tccctgatct	ctacctacta	aatgccagga	gcaacacagt	240
acctccagct	cagttgtgac	aactactgaa	tgtctccaga	caactactga	atgtctccag	300
acattgcaga	gaaattgagt	ctggttgaga	agtcactgtt	ttagggcata	atttttgggt	360
agactgttag	attctttgtg	ttcgttgtnt	ctggcctgta	taactcttct	taattatctg	420
ctactcaaat	gtattttggga	tcagccactg	tcttccattt	ctcttttgct	cacagatcta	480
ctccacagct	cttctccctt	caaacactgt	tcctcagcat	cttggtttttt	gcagccaaac	540
at						542

&lt;210&gt; 48

&lt;211&gt; 1495

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 48

cggcacgagg	ctacttatat	tttatgaagg	acattttttg	ttagatgata	tcacccctctg	60
tgttatttgt	tgattgggtt	tgttttttgc	ttgttggttt	gtttgtttct	tccatgtaag	120
gaaaagtagt	gtaagcagta	ggaagaaaat	gaggaagatg	tattttgcat	gttcttcctt	180
tcaatgttct	tacacattgt	attactgcat	tgtggtaata	gcttctataa	aatctgccat	240
agctgggatt	atgcagcttt	gcaagaatct	actagatttt	attctaactc	atattagctt	300
gtcctatcaa	cttctggaat	tatctaatta	ttgcttttaa	aagtttctctg	cctttcaacg	360
tttccctgct	atgcaaaacc	tttcccagac	cttggtttct	taaaagaaag	atgttgctac	420
agttcccaat	tctttcttat	tacaggctca	ggtgtacagg	ttattctggc	ttaattttat	480
ctaataagc	ccattccctt	ttgtacatga	agatgtcact	taaacctatg	tttacaact	540
aaagagacta	atcactcaat	atgaaaacat	gaaaacattt	ttgcttaaaa	tattaagatg	600
gaaatagtta	aatatggatt	attttgtcct	tttacttttt	aaaaaaagtt	acatattgta	660
tgcactgtgc	tgatgcaaga	attctacatt	ttaatgaatt	ataaaattat	tctgcatctc	720
atcacgtcac	agtattttctg	ctctattttat	tcatatacat	agaaatatat	atgggcttaa	780

tcatttataaa	tttggtgcag	caagaactct	cctacctgta	ggcaatagat	tgctatgttt	840
tcaacaaatt	gtggcaaatt	ctaaacagca	attcttttgt	acgtaatagg	acatttcata	900
ctagaaaaat	aaagtaatgt	ttttgacatt	ggatttggtg	cagtttctaa	tgaagcaatg	960
gttggttggt	taatattgtc	tctgtagctg	ttagcattgc	caaattataa	agggtaaatt	1020
ttatggaaat	cctgagacca	ggaagatata	aatttcattg	gtacttaatg	gtataaagtg	1080
ttttacagtt	tctatcacca	tacaaataca	taaagacatt	ttatagtttt	atcaactata	1140
gagcttttagt	ctttcaaaaag	taatttttga	aaaacataca	ttcctggcca	ggtgtggttg	1200
gccacgcctg	taaccccagc	actttgggag	gccgaggag	gggggatcac	ctgaggtcag	1260
gaatttgaga	ccaacctggc	caacatgggt	aaacccatc	tctactaaaa	gtacaaaaat	1320
tagccaggca	tggtggcagg	cacctgaaat	cccagctact	agggagggtg	aggcaggaga	1380
atcacttgaa	cctgggaggt	ggaggttgca	gtgagccgtg	atcacgccat	tgactccag	1440
cctggggggac	aagagtgaga	cttcattctca	aaaaaaaaaa	aaaaaaaaaa	aaaaa	1495

&lt;210&gt; 49

&lt;211&gt; 818

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 49

aaaacttgag	tatgttgagg	gaaggaatat	atatatatct	gggagagaat	ggatacgttt	60
tgtttttctg	aatggaatt	agaaagatgt	tcagttgtct	tgtgcattct	tgcaaacctt	120
gcagttttga	gagccctgtt	tctgccttgt	atcattttcc	actgtgtatc	kgattctagg	180
agcgtgaaca	gggagacaaa	ggtgaagtgt	gtgcacacct	ctgtccatgg	ggtgggtcat	240
agctttgtgc	agtcmgcttt	caaggctttt	gmccttggtc	cycctgaggc	tgttcctgaa	300
cagaaagatc	cggatcctga	gtttccaaca	gtgaaatacc	cgaatcccga	agaggggaaa	360
ggtgtcttgg	taacctaat	ttttttttaa	ttatgaaatc	tgcttttata	ttcaaaacta	420
ttactgtcaa	gtaaaataca	tttttatgtg	ttttcattgt	gctgaagaaa	aactaatttc	480
agcatggaaa	tatgtatgtt	tggtctgggtg	cagcgtctca	tgtctgtaat	cccagcactt	540
tgggagacca	aggcaggcag	atcacttgag	gtcagggtgt	cgagaacagc	ctggccaaca	600
tggcaaaacc	ctgtctctac	taaaaataca	aaaattagct	gggtgtggtg	gtacatgcct	660
gtaatcccag	ccacttgagg	ggctgaggca	ctagaattgt	ttgaacctga	gagatggagg	720
ttgcagttag	ctgagattgc	accactgcac	tccagcctgg	gtgacagggt	gacagagcga	780
gactctgtct	caaaaaaaaa	aaaaaaaaaa	aactcgag			818

&lt;210&gt; 50

&lt;211&gt; 1711

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 50

ggcacgagcg	ctcctgtcct	gccactgagg	gacccgggta	ccaaccctca	tgtagctcag	60
tttgcccatc	tgtcccgggtg	ctaacacaca	gttctcgga	gactttcccc	attcccagag	120
gagtagtgcg	aaatgcgtgt	acctctagtc	ttaagctggg	cgtttgatt	agttgggttt	180
tctgggtgtc	atttagcaag	tgaaagtttc	tggttccctc	cttactgtg	tgacctgact	240
agtcctcctg	gattgcattt	atggaagtgt	atacgagacc	tagtttccat	ggaggaactc	300
actgattccg	cgaggagat	gggtactgg	atgatggtct	tcagccttaa	ggctatgttt	360
ccagtgtcct	ctgggtgttt	ccaagagcgg	caagaaacga	ataaatctct	gacccttctc	420
aggtgcagcc	agagagacac	tagcccactg	atggacggac	agacgtgggc	aagggtccgt	480
gtcactaaac	caccaccac	tgccacagct	gcctacaaca	gacacatcag	atgacactcc	540
gggcaataaa	atgattttca	ctgaggactt	actggtttta	ataatagggtc	ctgggtgtaga	600
gaagtccctc	aacctattgt	gcaacgagtt	ttgagaagcg	ggtaagctgt	atgttttgtg	660
gtttttgttt	ataaattcat	ctacaggaag	accaatattg	actgaatgaa	gctttcattt	720
aaagagctaa	aatatgcttt	gtgtttttat	atgtggatac	tactttaaac	ctaacgacta	780

ttcattgtat	catagcttgt	gatgtattct	gctcatggct	tttaaggtaa	attgtgccat	840
gatccactgc	cattctaatt	gctttaacaa	gtcattacca	cactactgtt	acatcttaat	900
tatgcataca	gacaggtaga	cttggttttac	atatgtgaac	taactagttg	tcaaagcaaa	960
tgcagattgt	attctgcaag	taaagtcttt	ttctctctga	aatttctagg	gatgttcttt	1020
aagtgaatt	catattaaaa	ctgaagattt	tagttacaag	aactgagtg	agattaagtc	1080
tttgtgattc	aacatagtca	agatacaact	gtggatattt	catggaagta	tgcaataaaa	1140
tgtctctacc	tggaaaaatc	tatcaagcag	cgtcacagta	ctgaatttga	aaccagaaat	1200
actgggtttt	tatataaatg	cttcatagat	ttgttttatg	ataaagggca	cataactctc	1260
ctaaacctca	caccacctct	tgaataggta	taataagtcc	acatcaatgc	tgatgcctta	1320
gctattatta	aactcttaca	gtatgatgta	aagtgaaggt	acaatgtaag	atcattccta	1380
ggccaacttt	gaccagtttt	atacagaaac	atgtgccaac	ttttctgttt	gcaaggataa	1440
tatcaaagca	aacaccagaa	agttatatct	ttgatgcatt	ttttcaaaat	catacacata	1500
atacacaac	caaagacaaa	tgatgaatat	tacgtcagaa	aatataaagt	cttccccttt	1560
cttcttttgc	caagaaagtc	caatattttc	accattttta	tgcacacaat	caactttatt	1620
taagctggaa	gttaatgtct	cattgttttc	attgttctaa	ataaacacct	tttcccttga	1680
gtattgctct	aaaaaaaaaa	aaaaaaaaaa	a			1711

&lt;210&gt; 51

&lt;211&gt; 749

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 51

gccaaaccag	rtaataat	ctttataata	catgaagtcg	ttattttgca	tttattttct	60
taggtggcca	atgggggttat	cttgggggga	gacttttata	ctcctaaggg	acagcttggc	120
cattaacttt	caaagtttct	ctaaagcagc	gtcaggagat	atatttggtt	gtcatgacta	180
gtggcattcc	actgacatgt	aatgggtaga	ggctgggtag	acatcctacg	atgcacaaga	240
cagcctccca	caataaagaa	ctgtgtggcc	caaaaatatc	agtgatgctg	agattgagaa	300
acttaaagaa	atttaaaaaat	taactctata	caaaaatctaa	tgtttgagtt	ttctccatgt	360
atctgtgact	gcaatgacca	gagtgaactgt	ccataaagaa	agtgcctaaga	gttggctggg	420
tgcggtggcc	tacacctgta	atcccagcac	tttgggaggc	caaggtgggt	ggatcacctg	480
aggtcaggag	ttcgagacca	gcctggccaa	catggcaaaa	ccccatctct	actaaaaaat	540
acaaaaatta	gctgggtgtg	gtggcacgca	cctgtagtca	cagctactca	ggaggttgag	600
gcaggagagg	tgcttgaacc	cgggagatgg	agggtgcagt	gagccgagat	tatgccattg	660
cactccagcg	tgggtgacag	agtgaagaca	aaaaaaaaaa	aaaaaactcg	agggggggcc	720
cgggtacccaa	ttcgccctat	aggcagtc				749

&lt;210&gt; 52

&lt;211&gt; 1091

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1079)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 52

ggccagtggg	cagggtcaca	gggcaaggtc	cgcggggccg	ctgggtgcgg	cgacttccgt	60
gctcccggcg	agcgggcgga	gagcgggggc	cgcactgggg	agtgtgggct	gggccgcaga	120
tgtcatgtgg	cctgtktttt	ggaccgtggt	tcgtaacctat	gctccttatg	tcacattccc	180
tgttgccctc	gtggtcgggg	ctgtgggtta	ccacctggaa	tggttcacat	ggggaaagga	240
ccccagcccc	gtggaggagg	aaaagagcat	ctcagagcgc	cgggaggatc	gcaagctgga	300

tgagcttcta	ggcaaggacc	acacgcaggt	ggtgagcctt	aaggacaagc	tagaatttgc	360
cccgaagct	gtgctgaaca	gaaaccgccc	agagaagaat	taatggagga	cacaggggccc	420
tatggctcta	ctgtgggtgg	tgacttgctc	tgctaccatg	ttgacagagc	cccagaaccc	480
acatctaatt	ggctttgttg	cttattctgg	cccttcccac	accacacagc	cacacaaata	540
ctggctgctc	cttgatggcc	aggcagaccc	agcagcagcc	gagggggccag	tgaagaggaa	600
ggcgcgcatc	gttgtgtggt	ggccacaagc	actcaggcat	ctgagtttac	tggtgcaactg	660
ctgggaggag	agttatgaga	tgaacattgg	ctgtcaatct	ctgtgggcag	gcggtttggc	720
ctctagtggg	aatggctggg	atttgggcgt	tgcctttagg	agggatacct	gcatgtctag	780
ttccagtctg	cactggaaaag	aattcaaata	tgacactggc	tcccttcact	attttgccct	840
atcctttgtg	ctcattctta	ctgaaatctg	tcttgctcagc	tcaggaatgg	gattccccca	900
ggaaggaaaag	cactttttctg	ttctgggaag	cccagactgt	tcactttggg	gcagggacga	960
acatgtgcct	cgtgaatttg	cttgaaaaca	gtcaccatct	tctacccccca	tcactgtata	1020
gtgaaaaacc	tgattaaagt	ggtatctgag	aaccawaaaa	aaaaaaaaaaa	aaaactcgng	1080
ggggggcccg	g					1091

&lt;210&gt; 53

&lt;211&gt; 2254

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1182)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 53

ggcacgaggc	ccgctgcaat	gttatcatca	cccaacctcg	ccgcatctct	gctgtgtctg	60
tggcacagcg	ggtcagccac	gaactgggcc	cctccctgcg	ccggaatgtg	ggcttccagg	120
tgcggttgga	aagtaagccc	ccatcccagag	gcggggccct	gctcttctgc	actgtgggta	180
tcctgctgcg	taastgcaga	gcaaccccag	cctggaggggc	gtgagccacg	tcctcgtgga	240
tgaggtgcat	gagcgggacg	tgaacacaga	ctttctgctg	atcctgctca	agggcctgca	300
gcggytcaac	ccggccctgc	ggctgggtgt	catgaktgcc	acagggggaca	atgagcgctt	360
ctcccatac	tttgggtggc	gccccgtcat	caaggtgcct	ggcttcatgt	accagtcaa	420
ggagcactac	ctagaggaca	tcttggccaa	gttgggcaag	caccagtacc	tgacccggca	480
ccggcaccat	gagtctgagg	atgaatgcgc	actcgatttg	gaccttgatg	ctgatctggt	540
tctgcacatc	gatgctcgcg	gggaaccagg	tgggacccctg	tgcttccctgc	ctgggtggca	600
gagatcaaag	gagtgcagca	gcgcctccag	gaggccctgg	gcatgcacga	gagcaagtac	660
ctcatcctgc	cagtgcactc	caacatcccc	atgatggatc	agaaggccat	attccagcag	720
cctccagttg	gggtgcgcaa	gattgtcttg	gccaccaaca	ttgctgagac	ttccatcaca	780
atcaatgaca	tcgtgcatgt	ggtggacagt	gggctgcaca	aggaagaacg	ctatgacctg	840
aagaccaagg	tgtcctgcct	ggagacagtg	tgggtatcaa	gagccaatgt	gatccagcgc	900
cggggccggg	cgggcccgtg	ccagtccggc	tttgcctacc	acttgttccc	tcgaagccgg	960
ctggagaaaa	tggctccctt	ccaagtgcc	gagatcctgc	gcacacctct	tgagaacctg	1020
gtgctgcaag	cgaaaatcca	catgcctgag	aagacggcgg	tggagtccct	gtccaaggct	1080
gtggacagtc	caaacatcaa	ggcagtggac	gaggctgtga	tcttgctcca	ggagatcggg	1140
gtgctggacc	agcggggagta	cctgactacc	ctggggcagc	gnctgggtca	catctccacc	1200
gacccccggt	tggccaaggc	cattgtgttg	gctgccatct	tccgttgccct	gcacccacta	1260
ctgggtggtcg	tttctgcct	cacccgggac	cccttcagca	gcagcctaca	gaaccgggca	1320
gaggtggaca	aggtgaaagc	actgttgagc	catgacagcg	gcagtgacca	cctggccctt	1380
gtgcgggctg	tcgccggctg	ggaggaggtg	ctgcgttggc	aggaccgcag	ctcccgggag	1440
aattacctgg	aggaaaacct	gctgtacgca	cccagcctgc	gcttcatcca	cggactcatc	1500
aagcagttct	cagagaacat	ttatgaggcc	ttcctgggtg	ggaagccctc	ggactgcacc	1560
ctggcctccg	cccagtgcaa	cgagtacagt	gaggaggagg	agctgggtgaa	gggcgtgctg	1620
atggccgggc	tctaccccaa	cctcatccag	gtgaggcagg	gcaagggtcac	ccggcagggg	1680



aagttcaagc	ccaacagcgt	cacatatagg	accaaatacag	gcaacatcct	gctgcacaag	1740
tcgaccatta	acagggaggc	cacacggtta	cggagccgat	ggctgacgta	tttcatggca	1800
gtcaagtcca	atggcagcgt	cttcgtccgg	gactcctctc	aggtgcaccc	gctagctgtg	1860
ctgctgctga	ccgacgggga	cgtgcacatc	cgtgatgacg	ggcgccgggc	caccatctca	1920
ctgagcgaca	gtgacctgct	gcggctggag	ggtgactcgc	gtaccgtgcg	gctgctgaag	1980
gagctgcggc	gggccctggg	ccgcatgggt	gagcggagcc	tgcgcagcga	gctggctgca	2040
cttcccccca	gcgtacagga	ggagcacggg	cagctgcttg	cgctactggc	agagctgctg	2100
cgaggaccct	gtggcagctt	tgatgtgcgc	aagacagctg	acgactgagc	cctgcttctg	2160
ctggggctgt	gtacagagtg	caaatgttta	tttaaaataa	agttctattt	atcccttggt	2220
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaact	cgag			2254

<210> 54  
 <211> 486  
 <212> DNA  
 <213> Homo sapiens

<400> 54						
cacactgaca	tctccccaac	aggtgagggc	agggagagct	ccagacaggg	agaggccttc	60
agagaacagg	aaggaagctc	cctccctcct	ctgcattttg	cagcctgtag	ctcacgtgcc	120
ttttatgccc	cacatctcat	tctgtctggg	gactccatac	gtagtggctg	tctaccttcc	180
cgcgtggatt	gtaatgcttt	tgctaccagg	ggtcaggcca	tactcatcac	tgcaggccct	240
gaagcatcca	tcatgttcct	cgagctcagt	atgtgctccg	tacatgtagc	acagtggaaa	300
aacttgagct	ttgctggcaa	agacagacag	aatgagcttg	aatctcagcc	cagctatggc	360
ttttctagtc	ctgtggctag	aaaatgactt	agcctcttgg	actttgggta	acccatctgc	420
aaaacagggg	tggcaccac	ctcttagaaa	gttacagtgg	tcaaaaaaaaa	aaaaaaaaaaa	480
ctcgag						486

<210> 55  
 <211> 1270  
 <212> DNA  
 <213> Homo sapiens

<400> 55						
gaaaccatcc	aagataagag	acatgggagt	gaaattcaca	cccactctgg	ctttcatacc	60
atgggtctga	acattagccc	atggtgtttc	ttggccatac	tgacctgtgc	catttcagct	120
gcattcatct	cagttggtgt	tgtctgctgg	ctgctctttc	tgatttccca	caggagcagt	180
aagaacctga	ggaagagtag	ggtcagagga	gtctgggaga	atgaggaaat	atgagagccc	240
caggaactga	aaaggcctgt	gagagactct	gagcttcctg	ggaacaggta	taggttcttt	300
ttatttcaat	aataacagaa	acaactgtca	aaaccatgtg	cctgtactat	ttggagtgtc	360
gtccttgag	aatctcatta	taagaacctt	aggaaatagg	cacatcatct	cctggataga	420
atcctaggaa	atgggcacta	taatgggcac	tttatcccat	tttataaaca	tggaaattga	480
ggcacagaga	gattaagtac	tttcccaagg	tcatacagct	agtgatggag	gagctagcat	540
ttgaacccsg	gagtttttag	tctattgagt	ttaaccgaca	gatcatactg	tgttttggta	600
gggaggragg	gtgaagcaag	caartgaaca	aatgartctg	ggatttarga	cttgccagac	660
aaacaaggcc	caagaggcaa	gtgtgcaggt	gggtgtagtt	gggagtcagc	agagttgggt	720
tggaattcaa	gctttgccac	ctgctggcta	taaaccttgg	ttgggtaagt	aaccaaggt	780
aatgagatc	atctctgtaa	aactcttagc	cttgtgcctg	gcacatagta	aatgcttaat	840
aagggttcac	tgtaggtatt	actgttactg	ataacataca	aatagattgt	attaatggac	900
cataattgca	actgtataaa	acaaattcca	tgttttggcca	ggcgcagtg	ctcaagcctg	960
taatcccatc	acttcgggag	gccgaggtgg	gcagatcacg	aggtcaggag	atcaagacca	1020
tcctggctaa	cacagtga	ccccatctct	actaaaaata	caaaaaaatt	agccaggcat	1080
ggtagggggt	gcctgtattc	ccagctactt	gggaggctga	ggcaggagaa	tggcgcgaac	1140
ccagggggcg	gagcttgag	tgagctgtaa	ttgtgccact	gcactccagc	ctgggcgaca	1200

gagcgagact ccgtycaaa aaaaaaaaaa aaaaaactcg aggggggggcc cgaacccaat 1260  
cgccctatag 1270

<210> 56

<211> 2059

<212> DNA

<213> Homo sapiens

<400> 56

ggcagagacc	tcactgggta	aacacaagct	ctcggcaggg	aacaagctct	cggcagggaa	60
tgcacagaga	agcactaagt	caaagtcata	tccgtgtggt	cattaaaatt	ccagtgaatg	120
aaaaagtttt	agggaacatt	aactgttaat	ggcttatgta	ttagctgttc	tctgttttaa	180
aagccttttg	gcacttttca	aacctaacaa	acaactgatt	gaattttctat	tgatgggtcaa	240
agtggtaaaa	atacctcttt	gttatctaag	acaactttta	ggtggcatta	agaccccgag	300
ggtctagggg	cctccagggtg	tacggctttg	aagtaagggc	aagaagcatg	ggtgccctct	360
aggagcactg	ggagggacag	tggaggaaga	ggccccgccc	gggtgccact	gctgaggcag	420
ctcttagggc	cctgccactt	actttgctca	gagcaaaagg	tgccgtcagc	tgggtcctac	480
ccccgcctgt	gcggctggat	ctgggctgcg	tcagcaccgg	gacccgcccc	agcagcacat	540
ctgtcaaagc	ggaaaacagt	tcacacacca	gagcctcatg	tggaaagagt	ccaggcgctc	600
agacttttct	ccttcacgac	cctcatctct	gctctcgggc	ctcagcccg	ctgtcgctact	660
gcaggaaatt	ttgtttcctg	cttgtcttca	aagacttcag	ggcttagaac	ggaccataga	720
aagatatgaa	ccgagagccg	tggcagctgt	ccagcttgca	ggctgatatt	tgtgtagatg	780
ccatgcagat	aacacagcag	ggtccaggcc	cttccctctg	gaactcacac	tcggctgtat	840
tttgggagga	accgctgggc	aggttctgcc	caggaacagt	taactctgca	gagcacagtt	900
tccacatctg	ggctgagttc	ccaaagaaag	tgcgcctaac	aacgtcttgt	ggaaggcggt	960
tggcgctcaag	agaagtaaag	tggtcagatg	gcagtgattt	taatgaacct	actagctatt	1020
ttaataggaa	agattttttt	ttttatccgt	ttgtttttta	tttttagaat	catgaaatag	1080
caagttggct	ctgctgaagt	agaaatgggtg	ggcggggagt	cgccactgac	catcgctctg	1140
gcagagcacc	ttcctgctga	ccacagctgt	gagcgccggc	tgtacgcagg	tccttgcctg	1200
gcgggtgccc	aagagggctg	agggtctgct	ctgccatggt	gtctccacct	tggacacccat	1260
gaatcatgag	aggttctcag	ggctgcctcc	cacaggcttt	ctgtgtctta	cctgggacac	1320
tcgggactag	ttgtgttttag	gttttcttaa	aattctgtag	taattgcatt	gtagagcatc	1380
cctaataccga	acttcagaaa	tccaaaatgc	tccagttagt	atttcatttg	agcatcatgt	1440
cagtgtctcag	atatggtcag	accctggagc	actttgcatt	ctgaagtga	ggatgctcag	1500
cctgcgtctg	acagaagctc	cagagaagtg	gctgcgagtt	cagggcaaga	ggctcctggc	1560
tttgaggctg	caccgtttct	ggaagtcaag	ccccacagt	gacctcgagt	ccctctgtga	1620
ataggaatgt	gctcgggcag	ggaacccgga	gcaccagccg	ctgggcccct	cggtccccgg	1680
ctctgcagcg	tctttcgggt	cctgtgggtc	tggctgtgcc	cagccctgct	gcccgtggac	1740
tatagtgtct	tggggctcctg	caggcttggc	tgtaccgggc	cccagtgcac	ggtggcaagt	1800
gcctgtgata	ccagctactc	aggaggctga	ggcaggagaa	tcacttgaac	ctgggaggca	1860
gaggttgcag	tgagcggaga	ttgcgccatt	tcactccagc	ctgggcagca	agagcgagac	1920
tttgtctcaa	aaaaaaagga	acgtgcctca	ttcagtgggt	cgatgggtgg	tctgatcaat	1980
gcccagaagt	tctgatggag	cttctgtcag	acacaggctg	agtatccttc	accccaaaat	2040
taaaaaaaaa	aaaaaaaaaa					2059

<210> 57

<211> 868

<212> DNA

<213> Homo sapiens

<400> 57

gactgactat	agggaagct	ggtacgcctg	caggtaccgg	tccggaattc	cgggtcgacc	60
cacgcgtccg	ctgaatttag	gagacttttt	acccaggggc	aaaaggctct	tagggtaatg	120

agatggatgg	tggcccaggt	gcattttcca	gggcctgggt	tctccagatc	ccgtggcttc	180
tgttgagtgg	aggcaacttt	gctctgtgtg	aacctcgccc	ctgtccctct	gccgggcacc	240
cctggcagga	agcaggactc	ccatcctcac	cctgacttag	actgtcctct	gagtcagctc	300
ctctccaaga	caggagtggg	cagccctggg	cagtcttctg	gccccttgct	aaagtgaggg	360
scaggaagct	ggggctgccc	tccagaaaagc	cggggtaggr	actctgaaaa	atacctcctc	420
taaacggaag	caggygtctc	cagttccact	tggcgccccc	tcccacaagg	cccttcctcc	480
ctgaggaccc	caccccccta	ccccttcccc	agcagccttt	ggaccctcac	ctctctccgg	540
tgtccgtggg	tcctcagccc	agggtagact	gcagtcaggc	gggatgggac	gggcaggcca	600
gaggtcagcc	agctcctagc	agagaagagc	cagccagacc	ccaaccctgt	ctcttgacca	660
tgccctttgt	gatttcagtc	ttggtagact	tgtatttgga	gttttggtgt	tcaaagtttt	720
tgtttttgtt	tgtttggttt	ttgttttgag	gggggtggggg	gggatacaga	gcagctgac	780
aatttgattt	tattttatttt	aacattttac	taaataaagc	caaataaagc	ctcaaaaaaa	840
aaaaaaaaaa	aaaaaaaaag	gcggccgc				868

&lt;210&gt; 58

&lt;211&gt; 986

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (592)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (669)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (767)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 58

gaaattaagt	catttagata	aaaatatgcc	attcttatct	gtttggtttt	ttaatcttgg	60
cttaatatatt	ggggttgagt	catttgtttt	gagagctgtc	ctgtttattg	caggggtgttc	120
agcaacatcc	cagatggaag	cagcatcccc	ctaccagct	gtgacaaaaa	gaaaaaaaaa	180
tgtctccaka	cactgccaaa	tatcttcttg	gggtgcccct	ggttgagaac	cactgcttta	240
gtggataaac	tttaggcagg	agggaaatga	tcgcagttag	atagttggag	gaatgtggag	300
caagggaagc	aataaaactgt	gaccataaaa	acatagaaa	atggcttata	tgtggatttt	360
tttttaaagc	acgtagaatt	gcttaaaatg	gacaacagca	gcatataaat	cagtggcaga	420
gttggtggct	gaatttagag	catcttaagt	ctatgttctc	ctggaacaga	gtgcagataa	480
ttcagttatc	agcttggtta	ggtgcatgtt	gaagtattta	gtcacacaca	aacagttaat	540
gtatggggaa	gataacttct	atactagtag	gagagaaatg	gaacaagaat	wntaaataca	600
ctatcaaaat	atgcaagaat	ggcaagmgga	aaaggcagaa	caagctgcaa	aacmcacaca	660
caattagana	taaatatttt	gggacacaa	aaatgtgaat	ggattaaaac	ctctgttaat	720
gacaaagttc	tccagttaaa	ggaaggcaaa	tagtggtatt	aggaatngat	tactatatga	780
tgattaaagg	ctcagttcaa	caggaagatg	attgatagaa	ctttcctaca	tttgtaacac	840
agtcttagaa	gatattaaag	caaacattca	agaagaaatt	gatcacctac	taccatagtg	900
tattttattg	aattggtaca	tttcaataaa	gtgtcataag	gcacggttga	aggaaaaaaa	960
aaaaaaaaaa	aaaaaagggc	ggccgc				986

<210> 59  
 <211> 695  
 <212> DNA  
 <213> Homo sapiens

<400> 59  
 ttttttttct tgaaataaaa tgggggagta atgggaaata atttttttga gcccttgctg 60  
 ttctaaaaat gtttgcattg tgccttcattg tttgacagtt cagttccagg ttgaaaatta 120  
 tttttctttg gaatgttaac agctgccctc tttttctgtg ttttatctaa tgttgctgaa 180  
 gagaaatctt ctgattctta ttcttttttt ggtgacctgt ttttaatttg tgtctttctt 240  
 ttttttcccc tgggaagcttt taggtctctc cttttatcct tgtagtctga gatctgacaa 300  
 tgatggttgt gtctagtttt ccccaggata ctttttcatt tgtcctgggc agcactagta 360  
 gatcctttca gtttgtgtac ttctgtttct cttgctctgg agaatttaaa aaatatatat 420  
 atttttgaga cagagtctca ctctgtcacc cagggttagag ggcagtgggtg tagtctctac 480  
 tcaactgcaac ttctgcctcc tgtgtttaag cgattctcct gtctcagcca cctgagtagc 540  
 tgggattaca ggtgcctgcc accacgcccc gctaattttt ttgtattttt agtagaggca 600  
 ggggtttcacc acgttgcccc ggctgggtgtc gaactcctga cctcagatgg tccacctgcc 660  
 ttggtctccc aaaaaaaaaa aaaaagggcg gccgc 695

<210> 60  
 <211> 314  
 <212> DNA  
 <213> Homo sapiens

<400> 60  
 gtcgaccac gcgtccgctt tgaggagcat tctctagat tgcacaaggg acagtgcctt 60  
 taaccaagcg aggagtccaa agctcaggac ctgactaccc tgagggcacg ctgacgcctc 120  
 ttcccagggg gatggggagc tttctgcacc cccagtggca tctcctcatc acgttctgtg 180  
 ccgtccttgg gaaaggcctg cattctgac cttccaggcc ctctgagcat ggaggggcac 240  
 tggggaaggt cccccagggg aggagcacgt tgctgagtaa agaggtgtta ctcaaaaaaa 300  
 aaaaaaaaaa aagg 314

<210> 61  
 <211> 734  
 <212> DNA  
 <213> Homo sapiens

<400> 61  
 gactgcttat atttggcatt gtcttttccc tggcactgcc actgtcacca ccatccccct 60  
 tctggatccc tactttaccc cttcatgctg ctctggtggc agtgctctctg ctgccatgct 120  
 gtacttgagc ctgctgctac agccatgcct gaagatgcag ccccttcctc tcttctctgtc 180  
 ccaccaata tgaccagctc taggttccat tacttctgga ctttgctcca aataaaactt 240  
 acacaatttt attccaaacc caggtctctt tctgcaacac ccgagaaaaa tattgggctg 300  
 caggagccag agaggagaga gagatttact ggtgagagtt gtaggtggga attgaaagcc 360  
 aagtcattgtc tttgccccac cagaaactca ctaggatgta cacaatgcca ctgtgatggt 420  
 kttaaaatat gtaactaacc tgcacgttgt gcacatgtac cctaaaactt caagtatata 480  
 taaararaga aagaactgst gatacacata tcatgaaaaa agaccaaata aaataaaaaa 540  
 ataaaaataa ataaataaaa taaaatatgt ccacaaatgc tttgatgttc ctttgtttct 600  
 tgatctgtat gctagcaaca caggttcatt ccgtttgtga aaattcattg agctgtgctc 660  
 ttatgagctg tgtacttctc tacatgtatg ttaaagtgtg acaagaactt cacataaaaa 720  
 tcatttttaaa aaaa 734

<210> 62  
 <211> 1410  
 <212> DNA  
 <213> Homo sapiens

<400> 62  
 ccgcctcctt gccgccccagc cgggtccaggc ctctggcgaa catggcgctt gtcccctgcc 60  
 aggtgctgcg gatggcaatc ctgctgtctt actgctctat cctgtgtaac tacaaggcca 120  
 tcgaaatgcc ctcacaccag acctacggag ggagctggaa attcctgacg ttcattgatc 180  
 tgggttatcca ggctgtcttt tttggcatct gtgtgctgac tgatctttcc agtcttctga 240  
 ctcgaggaag tgggaaccag gagcaagaga ggcagctcaa gaagctcatc tctctccggg 300  
 actggatgtt agctgtgttg gcctttcctg ttgggggtttt tgttgtagca gtgttctgga 360  
 tcatttatgc ctatgacaga gagatgatat acccgaagct gctggataat tttatcccag 420  
 ggtggctgaa tcacggaatg cacacgacgg ttctgccctt tatattaatc gagatgagga 480  
 catcgcacca tcagtatccc agcaggagca gcggacttac cgccatatgt accttctctg 540  
 ttggctatat attatgggtg tgctgggtgc atcatgtaac tggcatgtgg gtgtaccctt 600  
 tcctggaaca cattggccca ggagccagaa tcactctctt tgggtctaca accatcttaa 660  
 tgaacttcct gtacctgctg ggagaagtgc tgaacaacta tatctgggat acacagaaaa 720  
 gtatggaaga agagaaagaa aagcctaaat tggaatgaga tccaagtcta aacgcaagag 780  
 ctagattgag ccgccattga agactccttc ccctcgggca ttggcagtgg gggagaaaag 840  
 gtttcaaagg aacttggtgg catcagcacc cccctccccc aatgaggaca ccttttatat 900  
 ataaatatgt ataaacatag aatacagttg tttccaaaag aactcaccct cactgtgtgt 960  
 taaagaattc ttcccaaagt cattactgat aataacattt tttccttttc tagttttaa 1020  
 accagaattg gaccttggat ttttattttg gcaattgtaa ctccatctaa tcaagaaaga 1080  
 ataaaagttt attgcacttc tttttgagaa mtatgttaaa gtcaaagggg catatataga 1140  
 gtaaggcttt tgtgtattta atcctaaagg tggctgtaat catgaacctt ggccaccatg 1200  
 gggacctgag aggggaagggg acagatgttt ctcatgtcat aatgtcacag ttgcctcaaa 1260  
 tgagcaccat ttgtaataat gatgtcaatt tcatgaaaag cctgagtgtt ttgcatctct 1320  
 tgatttaatc atgtgaaact tttcctagat gcaaagtctg actaataaag acaaagccac 1380  
 cctgaaaaaa aaaaaaaaaa gggcgggccgc 1410

<210> 63  
 <211> 1231  
 <212> DNA  
 <213> Homo sapiens

<400> 63  
 ggcacgagtg aatgtcgagg agttccagga tctctggcct cagttgtcct tggttattga 60  
 tgggggacaa attggggatg gccagagccc cgagtgtcgc cttgggtcaa ctgtgggtga 120  
 tttgtctgtg cccggaaagt ttggcatcat tcgtccaggc tgtgccctgg aaagtactac 180  
 agccatcctc caacagaagt acggactgct cccctcacat gcgtcctacc tgtgaaactc 240  
 tgggaagcag gaaggcccaa gacctgggtg tggatactat gtgtctgtcc actgacgact 300  
 gtcaaggcct catttgcaga ggccaccgga gctagggcac tagcctgact ttaaggcag 360  
 tgtgtctttc tgagcactgt agaccaagcc cttggagctg ctgggtttagc cttgcacctg 420  
 gggaaaggat gtattttatt gtattttcat atatcagcca aaagctgaat ggaaaagtta 480  
 agaacattcc taggtggcct tattctaata agtttcttct gtctgttttg tttttcaatt 540  
 gaaaagtaat taaataacag attagaatct agtgagagcc tcctctctgg tgggtgggtg 600  
 catttaaggt caaaccagcc agaagtgtg gtgctgttta aaaagtctca ggtggctgcg 660  
 tgtgggtggc catgcctgta atcccaacat tctgggaggc ccaggcgga gaactgcttg 720  
 agccccagga gttcagaatc agcctgggca acatagcaat actccgtctc ataaaaatta 780  
 ataaataaaa agtctcaggt gaccaaaggc tcctgaagct agaaccaggt ttggataaag 840  
 attgaagagc cacaggccac tcttccctct gagccattgg gcctagtggg gtcattgtatt 900  
 gtaattgctc gcaggagag cagtcttttt ggtgtaatag tgggatgtct gcttagttgg 960  
 caggggttca gtccaaatgg aagaatattg ggaaataaac ctccactatc ctttatagcc 1020

agggactttt	ttcctattta	ttcataaaat	aaattatagt	taattatacc	cataaacact	1080
ttattttaat	ccagtgttct	ccgcagcctt	ttgtctattt	atatgtgtac	caagtgttaa	1140
acataattat	tattgggcat	ttgaactttg	tttttcttta	aagaaatgct	gctattaaac	1200
atatttgtaa	atggaaaaaa	aaaaaaaaaa	a			1231

&lt;210&gt; 64

&lt;211&gt; 612

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 64

ggtcgaccca	cgcgcccgag	cattttgtctg	tataatttta	gttattgaat	taaaatcttt	60
tgggaccca	acaggatgag	atcattggcc	agctggcttc	ctccacctg	cacctggact	120
gaaattcccc	gtggcattag	aggtgtttcg	taagggtgctc	cctgctgtct	gtcctacaga	180
ttgcagtggc	tctgctggaa	aagaacggaa	ttctatgcaa	gttgcggtgtg	tcatgaagg	240
ctctgcacag	tgggtgtgtt	tctttgtcgt	ctttctcca	ctctgctctt	ctgtgaaatg	300
tgccagcagt	ggacagaaca	ggggcagagg	tgatcagtga	ccattgcaca	gaatatcagt	360
aagtgttgta	aggtatatag	tcttggccaa	caaattgtaa	gcaaaatacc	aggaaactcc	420
taatctagta	ggaaattttg	tatgcttttg	acaacatct	gacccactg	acactgaaag	480
tccttagaag	gagaattgct	tgaaccggga	aggtggcggt	tgcagtgagc	caagatggcg	540
ctactgcact	ccagcctggg	caataggaat	gaaactccgt	caccaaaaaa	aaaaaaaaaa	600
aagggcgggc	gc					612

&lt;210&gt; 65

&lt;211&gt; 2270

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 65

tttttttttt	aactttttta	acaatccatt	ttaatcatct	aaattattta	caatacaata	60
acatggattc	atccttttta	agacatggga	ttgtaaaaat	caacaagtga	atgatgcttc	120
aaataataca	tttaaataca	ttaatcaaat	tttttcagtg	cttaaaactt	tttctccatg	180
ggacagcagg	ctctggacaa	aagtgcctag	catacaagtt	ttcccaattt	ccttctatca	240
taccagctgc	acataaaaag	gttcatcacc	tcctgtctcc	aaagtgtctc	cctactgagt	300
gttcccaggc	agacaatagt	tcctgggata	gtgctgtttg	gtaacagaaa	agcccaagcg	360
tagaggacgg	attaaaaggc	agggaccaga	ccgccatgga	tacaaatccc	aagacagagg	420
atgccccatg	ccttccccat	gaagcttate	tgtctgcctg	tgtctccatg	attgcaggca	480
tagagctact	tgggacctcc	aggatgattt	acttagcgat	atgcttttta	cattctaaga	540
atcaaaatgg	tcctgttaatt	cccaatagag	aaaatagagc	caattcattg	ttctccctc	600
tcccctctga	agccagtttt	taaagatgag	ccttaccag	aaaataagcc	ccaaagaact	660
ctcatctaaa	tgatcagacc	cttctaaat	tacctttggc	aacctaggta	attctttttt	720
attacacacc	tccaacctga	ccctttctac	agtttcaact	ataaatgttc	atgcccctcr	780
tcaaataacg	ttgctaggat	gaatttgcca	caggtttgag	tacagagaga	acaagcaaga	840
aaaatgtcag	tgttttatttt	aaggagagtg	gccaggatgt	cagtcctcat	aattgggtccc	900
ttctctctct	ctatcctcca	aggtaagtgc	tttgttgact	tgataagctt	tagtccttct	960
gtacaacttc	tagaagatgc	acttaatggt	gcttctttgc	acttcagaa	ctcaccttct	1020
attctacctg	taaggctgta	ggggagcatc	ccaatcaaca	taaggcctac	cccttttagcc	1080
acgaaaatca	gccaggcatc	atgtttctgc	accaccacct	gccttctga	cggacactgg	1140
tgctgatgac	aaaaatggga	cagtaccgca	gctggtttct	ctttttcgag	tgtgtagata	1200
agaaataaaa	aacattttca	ttccctcaca	agcttaatct	agtaataata	ctgcctaaaa	1260
aaaatcaaac	cataaataaa	cctatgtgct	aaacaaatca	catgacttga	tgacttctct	1320
aaaattaatg	tcaaggaaaa	aaggaaaagt	tgatcccaag	taaaatccct	tgaccacagc	1380
tgtctgaaat	tagccagggg	aatgggagac	accaccaaga	acctcagctc	tttctgccc	1440

tgtattttcaa	ggggagtgtt	gtggccttca	caaataaaaa	ttatgaatca	caaagataaaa	1500
cgctctcact	tctaacctgg	tgaatcctca	ggaatgtcat	gaggatgaca	acacagggtt	1560
aattcatttt	ttctcagtct	ccccctgac	tccacaaaag	ctttgccttc	ccaacacaag	1620
gggctgggag	gtccagtcta	gacagagcat	gctgttgggg	taaacagtaa	ccatgtgatc	1680
ccatgattcc	cagagctctg	agcacaaagc	ttttcatccc	agtggcaact	ggaatgtggg	1740
taattctgta	aactcatggc	cacaccttta	atgcttgggg	acagtgggtg	gagtcagcca	1800
gagctctttt	ccaacttcat	ctagggtctt	ctctctggaa	aagcttagtg	acgttctccg	1860
aaggttttatt	tggttaagga	gtattgctaa	aacacttttt	aaaaatccac	tttgaacaca	1920
tgtgtaagct	gaaaagaaaa	tgacatatat	acctccattg	aagctgggaa	agtgaaaagg	1980
ctgacgaaat	gtctgaaatc	ctgagccttt	cctggttcta	ttttaatata	gcgtacaggt	2040
aacagatgat	ctcattttacc	ttctgaatga	cccagcactc	aatttcccta	aaactgctca	2100
gctccacttg	gaaatcacca	ggggacttga	gaatcttccc	cttagactca	gggagacacc	2160
cagaccagga	agaagggcac	tgatgttttc	agggacccaa	aagcccactt	tttttttttt	2220
tttttttttt	ggaattcgat	atcaagctta	tcgataccgt	cgacctcgag		2270

&lt;210&gt; 66

&lt;211&gt; 1283

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 66

ggcagcagcg	agggaaacaga	ttcccagggt	gggggtgggg	agggtctgggc	ctttgtctct	60
ttgtctcctt	tcccaaggca	aagtgaagag	aagagagtga	ctccttcttc	actcagggaa	120
cccaggcagg	gatgaagcgc	ctgtggtgtc	tgagctgggt	cccggggctg	caggggagcc	180
cctcagtgtt	gtcctctgta	ttcttctccg	tgttcaaacc	acagctgcat	tggacatgca	240
gtcaggtgtc	ctctcactgg	caccttccct	gccttttcat	tcttttttct	ggatagtctt	300
tcacaaagtt	ttctctgcct	tcaccttget	cttcttgaat	cagttcacct	tgaggggggt	360
taacagagca	ccttggcagg	ctctgttccct	ccagggtccca	ggccagcccc	cgggactcag	420
ggcctgcctt	cccctcacct	tcttgagcag	cacaaactcg	ttctctgctg	ctgtccgctt	480
gttgatttcc	tcctcatacc	tgtgggaatg	gagagggctc	attggttaat	atctcactga	540
aagcccttgc	tttcacaggg	cagcgttaga	caaggagcag	cgtgtccatc	agaagatata	600
ggtgctgggg	gccgcagagt	actgggcagg	ggtaagtggg	ggaaggcttc	ctggaggagg	660
gaacatgcta	accagttttg	agaatgaga	ctgttaaaga	tccagcttgg	caaacgagga	720
aggagcacat	ggagcgaatg	ccctgtggga	ctctcagagg	aaccaggatg	tgaactgccc	780
tccccaaatt	tgagtacagc	tttacaattg	acaaagcgct	ccaatctgca	tttctctcagt	840
tacccttgag	agcagtcttg	gagccagatg	cacttaaccc	tcctcttaca	tgggagagaa	900
cgtgagtggg	ttccccaaac	attccctaaa	cccagagcca	gagataaccc	tctgcccact	960
gcccagctca	ctgggcattt	gtcctaagag	tcaggccaga	ggctggagga	gcagagagca	1020
agttccagag	ttttgttggt	gtgactctgc	ttgatatgac	caagaacaat	gccctccact	1080
gacctccaaa	gcattttaagc	tggggtgact	gccaggggtc	ccttggaggg	acaagggcag	1140
ttgtccagtt	acaggggggac	tcctcctgct	cacctcttct	tgtagtcctc	cactacgtcc	1200
cgcacattcc	tcagctccga	gtccagcctc	accctgtccc	cagacagcgt	ctccagctgc	1260
ttccgcaggt	tgctgatgta	gcc				1283

&lt;210&gt; 67

&lt;211&gt; 1263

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1256)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 67

gaggagatcg	ccacctccat	cgaacccatc	cgcgacttcc	tggccatcgt	tttcttcgcc	60
tccatagggc	tccacgtgtt	ccccacgttt	gtggcgtaac	agctcacggg	gctgggtgttc	120
ctcaccttgt	cagtgggtgt	gatgaagttt	ctcctggcgg	cgctggtcct	gtctctcatt	180
ctgccgagga	gcagccagta	catcaagtgg	atcgtctctg	cggggccttg	ccaggtcagc	240
gagttttcct	ttgtcctggg	gagccggggc	cgaagagcgg	gcgtcatctc	tcgggaggtg	300
tacctcctta	tactgagtgt	gaccacgctc	agcctcttgc	tcgccccggg	gctgtggaga	360
gctgcaatca	cgaggtgtgt	gcccagaccg	gagagacggg	ccagcctctg	atggctcgga	420
gatgatggac	cgtggaaggg	aagcgtctgt	ggggagttag	cgcttagatg	gccagcagct	480
gctccttctg	ggaagctcgc	accttggtca	cagaacagcc	ctctagcaga	gcgtcagtgc	540
agtcgtgtta	tcccggcttt	tacagaatat	tcttgcctta	ttttagaatt	ttccggagta	600
gtttatttgc	agtctgttga	ttatgtgcag	tagaccgggg	acactgcgtt	ttaccgatca	660
ccttgaatgt	ggtgcctgga	tgtgcctttt	ttttttttcc	ctgaaattat	tattaatttt	720
ctattgtgag	ttcatcagtt	catagttttt	ttagtaaaga	agcaaaatta	aaaggctttt	780
aaaaatgtac	aacttcagaa	ttataatctg	ttagtcaaat	atttgttatt	aaacatttct	840
gtaatatgaa	gttgtaatcc	tggccgtgag	cttggaagct	tacttttgat	tcttaaagcc	900
tatgttttct	aaaatgagac	aaatacggat	gtctatttgc	cttttattgt	aactttttaa	960
tgaaataatt	tcatgtcaat	ttctattaga	tatatcactt	aaaatatttg	gtttttaaate	1020
acaagaatat	gtattcctta	ataaagataa	tttatgatca	tggataaatt	aattgaaatt	1080
tattaaaatc	tgtttttatt	aaaaaaaaaa	aaaaaaaaac	tcgagggggg	gcccgggtacc	1140
caattcgccc	tatagtgagt	cgtattacaa	ttcactggcc	gtcgttttac	aacgtcgtga	1200
ctgggaaaac	cctggcggtta	cccaacttaa	tcgcctttgc	agcacatccc	ctttgncagc	1260
ttg						1263

&lt;210&gt; 68

&lt;211&gt; 1617

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1578)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1586)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1605)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 68

tcgacccacg	cgctccggga	acctgatact	gcaacctgca	atgtaggatg	tttgtatggc	60
atttaaagggt	aatgggtgatg	tttattattc	tatactttgc	atactgtgag	agtaattttc	120
actctgtctt	aagtgtgagt	aagcctcttc	taaaaatctt	gttcttgcca	agaaatttat	180
aaatcacata	cgaagacgtc	tgttgctaac	agttaacttt	atgaggtaac	tatatccttc	240
tatttctctg	gactcatttt	taaaaaatat	gccgaatact	gcatactgtt	taaggtagta	300
tataagttta	tgagagaagt	ggagagcttt	cttccttgaa	aagtcggtat	ttgttgagat	360
accatttgcc	tcacagagag	gtgttcccca	ctcccatccc	cattgccaga	taaataaata	420
ttttgagaaa	agtgacctaa	aacagctgga	aatcttaggt	gcactctgtc	gcagacctcc	480



ttaagcaggc	tgtatcttac	aattccctta	ctgcactggg	taagtgttaa	cttagttttt	540
gttttgccct	ttgctttaaa	tattctccaa	attaccattt	atgcaacatg	gttaggggta	600
atactgcatg	gtattcattt	acttgtttca	tgaactttcc	agtactgtac	aagggtcaaca	660
aagtaatgcc	tgtgggatcc	tcattcttca	cttttttact	ctgtgggttt	agcacagtaa	720
gggtactgcaa	agaccttcct	tccaaatgtc	tccttgactt	tattccttgg	gccaatcag	780
tatcctcaac	atcctaagat	tttgttgttt	tatcactgac	ctgtgggttg	cctgttttat	840
tctaattttcc	agaaaagttc	aatcccagta	tttgcaatat	caaataactc	taaaaccgat	900
gttgtgattc	taccttcctt	actattttta	ctgggcaaat	gccctatttt	tttaattatt	960
attattttta	acttttggga	cacacaaaaa	tcagcaattc	tcatgaagcg	tttgtttagtg	1020
tggcagactt	gtctaattcc	tgaactcat	tcattccctt	gagccagcca	atggggagga	1080
ataggataat	gcaaacacat	gttttggttt	ctcattttca	aataatttac	catgttaaaa	1140
taaacttttc	tttggttttt	atttgtagag	tcagctaagt	acccatattt	aaatgccgtc	1200
tttattattt	ttttgaggtc	tttggttttg	tctgtttttg	ttttgttttg	ttttgtaaat	1260
aaggtaactg	ggcaatcaaa	caccttttgg	ggattctggc	tttagtattt	tatcagccat	1320
tttaaaatta	aataataaaa	tcctttgtaa	gaaacttgca	tcctaatttt	tctttattgc	1380
aattgaaagt	gtaaataata	agacaatgta	agtaagacct	tcctaattgtc	taatacaaac	1440
tgggcttcag	caagtggcct	atttttatta	gggttttgaa	aggttgtgtg	tgtgtgtgcg	1500
tgccgtgtgt	gtggttttct	tttttaaatg	gatagtagag	tgggtggctgg	ataagggtac	1560
ctgtaatggg	ggtttggnca	gcaagnctga	aattttatact	tttgnaaata	aaactac	1617

&lt;210&gt; 69

&lt;211&gt; 1389

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (755)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1177)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 69

gcttttttag	gcattcattg	gacacttgct	ttaataagaa	tagttttctta	gttggcataa	60
tgcttctgaa	gtaatggtag	tttaaaataa	tttatctcat	gaactttaag	cattcctctt	120
gaaatcttgt	ttttactcta	tctagtcagc	ccttataggc	aatccaaagg	gatgctttgg	180
atgcttttagt	ccagtgggtc	tcagagagtg	gtctgtggag	tcctggaagt	cgctgagacc	240
ctttcaggca	atttgcaagc	tcaaaactaa	tttcagaatg	acaccaggat	gttctgtgcc	300
ttttttgctg	tgttggctat	ttgcactgat	gatgcaagag	aaatggggag	gagtaaaatc	360
actggtgtct	taccactatt	caagacagtg	gcaccaaact	gtagtagtct	agtaggcatt	420
gtatcctgca	cagcctcccg	ccaggagtgt	gatggaagac	caaggaagca	gtgtaaattg	480
aggtacacgg	gaagcacttc	ctttgcaccg	tgaaggatga	tgactgtttt	aaggaaaagc	540
acttatgcca	tgggtttgtg	cgtgagctga	accagctgcc	tttttcatgg	aacatgactt	600
ttacttgaaa	gagtaactga	cagaaaacca	attattctga	cttgtgtttg	tagcagacat	660
tttcttgaaa	atgaagaagt	gggtctgtga	cttcaggaaa	atgtctgaca	gtatctgttg	720
ccaaagaaaa	tgtgagtttt	caagccaaga	atagnaactc	agaaaacttg	tattcmcttc	780
catgggcttg	atgmccctct	agtacttaga	cctttctgac	gagataagcg	gtggcattaa	840
caaatgtgac	gtttttcatg	ttatctaaat	acatttgtca	acatttrraa	gatctgcaca	900
actccctgga	ccaggattty	ccaaatgatt	gttgcttttt	gttacaaaat	cagggaatag	960
atagaagatt	cattcaaata	atgaaagata	gactgatgga	tttttatgta	acagaatagg	1020
aaaagtttat	gacatgtttt	cagattccac	cttgcaacta	atttttaaga	agctaccact	1080

tgtagccag	gcacagtgt	cacgcctata	atcccaacac	tttgggagtc	caaggtgggc	1140
agatcacttg	aggtcaggag	ttcaagcctg	gccaacntgg	tgaaagactt	ctctactaaa	1200
actacaaaaa	ttagctgggc	atggtggtgg	gtacctgtaa	tcccagctac	tctggaggct	1260
gaggcaggag	aattgcctga	gcctgggagg	cagaggttgc	agttagccaa	gacgcgcga	1320
ctgcacacca	gcctgggcaa	caagtgcgaa	actctgtctc	aaaaaaaaaa	aaaaaaaaaa	1380
aaactcgag						1389

<210> 70  
 <211> 1896  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1802)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1856)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (1886)  
 <223> n equals a,t,g, or c

<400> 70	
aaaacaaaaa agctaataat ctctcaagc aatttctggc ctaatagaat tatagtagac	60
agtgaagtat ctaaaccag ggaatcagat tgaggcacca tgtccatcgc cttgagaatt	120
aataggctgc atttctgggt tctccttttt tttttttttt ttgcccaact gagtctttct	180
gtggacttac atggaacttc ttattctctt aaatcattaa gttacttgac aatattcttg	240
gatttggaga aactggatgt agggccgtat gaaaaaatca ttcgaaatca gatttagggg	300
tataaggttg gataggaatg ttttagaaag aagaatgtaa ggcagataac taatttgtca	360
catccaaagt ataaaactgc tactttttcc ctagaaaagg gaagctcatt ttaggcagcc	420
taaaccagta agattttctt cctcctccaa gtgcagattt ttgtacctt cgtttgtcaa	480
aacattcttt ggccctatgc atgccagagt gatatagaaa ggaagttacc acattttttt	540
gagaacaaat cactcctgat aaaatttctt agacaattga taatcatttt aagaagaaat	600
ttaattgtat ttagctctgt gtctcgcccc tttgggtgtc ctcttctacc tcttccatca	660
ctatagctaa atatttagaa gtatatcttg acacctagca caaatgtttt ggttaagtat	720
cttaaaaactg atggatggta tggctggggc agcatggctc acgcctgtaa tcccagcact	780
ttgggaggcc aaggcgggtg aatcacctga ggtcaggagt ttgagaccgg cctgaccaac	840
ttggagaaac cccgtctyta ctaaaaatac aaaaattagt csggtggtgg cgcatgcctg	900
taatcctgtc tactcaggar gctgargcag gagaattgcc tgaacccggg argcarargt	960
tgcartgagc tgaratcgtg ccattgcact ccagcctggg caacaagagc aaaactcagt	1020
ctcaaaaaac aaaacaaaaa acctgttggg atagtacgaa agaaacgtct tgcagttttc	1080
tggtgcagag aattaattag aaccaacctg ttggattata cacattcacc tttcagaatc	1140
ctttcttctc tgtggaaacc cacactctca gcagtgtgtg ggaacacagt agattcttaa	1200
ggaatgcttg ttgaatgttg cagtctgcat cttcttgaag taacagaact gttggtagct	1260
gtttaaaagt aaaatgtgtc taaagacctt ttggaaatta agatgtaaga gattaatgca	1320
ccaaagcagt ctcttaatta cttaaaatga attatttcaa agaactcttta attgaatttt	1380
ctgtgaagtc tggaaattgt aaattatgtc cctttgttca aaccagcccc tgaaaagaac	1440
aattaaggca attaatagat cattaaagtt ttcaatgaag ttggcatttt cygtgtatta	1500
agattagatg ttagctgctg aagtttgttg aggtcggaca taaagcttcc aacatcagta	1560

atgcaaaatt	gtcttgaacc	tgcgataaaa	ttttgttga	cttttttttc	attgcagtgr	1620
aaagggccat	gtagcatgcc	tcaaagccag	gttactcagc	ctagtccttg	tttaagcagt	1680
tttgatattc	atycaagttc	aattttcyca	cctgatttwa	kgattaattt	cctkggaaaa	1740
attttgaaaa	gttttccaaa	gaaagtaaaa	aatttaaata	atccggtaac	cccgtataat	1800
angaggatta	aaccttccag	gttccaaatg	gttttgggtg	gcaattttcc	cttcnaagg	1860
tccctttttt	ttcccaatgg	gtaatnaaat	aattaa			1896

<210> 71  
 <211> 308  
 <212> DNA  
 <213> Homo sapiens

<400> 71						
ggcacgaggc	ggcgctgcga	ggacccatgc	agctgacgct	ggggggcgcg	gccgtgggcg	60
cgggcgccgt	gctggccgcc	agcctgctct	gggcgtgcgc	cgtgggcctc	tacatggggc	120
agctggagct	ggacgtggag	ctgggtcccc	aggacgacgg	gacggcctcc	gcggaaggcc	180
ctgatgaggc	gggtcggccg	ccacccgagt	gagcgacacg	gccgtggggc	ctggcaggcg	240
ctggacagcg	cccgaggact	gggacattaa	acctgacctc	ccctcctcca	aaaaaaaaaa	300
aaaaaaaa						308

<210> 72  
 <211> 1688  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (912)  
 <223> n equals a,t,g, or c

<400> 72						
acccacgcgt	ccgctcatgt	ggacttatgc	cagtctagag	gcagaatcag	aaggcttgggt	60
tgaacatata	gctttccctt	tttcctctcc	ctccgcccc	cccagtacag	tccatctttc	120
aatgttgag	cctgggtgag	aaggagagaa	aaaggtggca	ggaatttcca	ggagatcccc	180
aagaatgctg	ccttgtctgt	ggacaaagat	ggacccatgtg	cccttcggaa	ttagggatag	240
aaacaaatat	tgtgtgctct	taacgattaa	gctgtgttat	ggtgggtttt	cagggtttta	300
ccctttttct	ttaccctttt	actctgcaag	aatggggaaa	gaatgcatac	tgcgaaaatg	360
agtcttttaa	attctgtctg	cctactagtt	ttaagtatat	ggtatgttgt	aaaatttcca	420
atgatgagag	acagcacaat	aaatgtacct	tatctcctta	ggctgaaggc	cataactaca	480
tagtggagta	atttaagaac	tctcttgcc	tcaccaaccc	aaaagggtgc	tttttgatag	540
caactggcta	atgaattttt	aaaaagagaa	gaaaaatact	agttttcccc	tcttttggga	600
aatagatttt	aaatggctaa	actactagcc	ttaaaactac	tagtctataa	atcaactacc	660
acttttgtga	atctgacagg	ccacattttt	atatggccct	ttacagaatg	gagtgtgttg	720
aacaggatac	taacgccatg	gagttgagct	gggcctagcg	atggaggggac	actctaacac	780
aactttccct	cagctattat	gcaacagatc	agggaaaaag	atgggatgac	agatggggtc	840
agacagaaag	agcttctggg	aaacaagctt	acatagtctt	ttttaaaatg	cacaaagcct	900
cccagctaag	angtcacttg	gtttgggctt	cattaggact	ggagactttg	ttggagtctt	960
ttctgggaac	ttggagagtg	gatgatattc	aggctctgaa	acattcccag	cgctctcccc	1020
aggggtgccac	tttctcaaga	tgaaaactgt	gactgaaaaa	attaataata	aatgtttctg	1080
agctgcctgt	gttctccctg	tgtgggtgag	agaagggact	agactcctaa	gcctgcctca	1140
gatacaagag	ggatcatttg	ctccaatttt	agagaacttg	aaagcaaggc	tttgacaaa	1200
attttgagac	cctaatact	ttaccttctt	ccaaattacc	caacatacgg	taaacaacat	1260
ttgtgcagaa	gtatgtatgt	atttagttca	ggttgacttg	tgtccttata	aactgttact	1320

caaattgattt	gaactttttat	gcgactggga	tttttttttt	ccaaagctac	aagcatggcc	1380
gcctgtggta	tcgaggtgtt	gcaaacaata	tctgtgttgc	gcttcctgtt	ttaacctacc	1440
tcgttttgtt	tgtttttgtt	tcactgttca	tcacagcagt	gttatctcca	ggagacatat	1500
agagagctca	accggcaatc	tcaggtgcat	ttaacatttt	taaaacgaaa	cagtagttga	1560
ccaaattttt	cttcttaaaa	aattggaagt	ggggggaatc	caatgacaaa	aactaatgtg	1620
gcttgtttct	ggagaaaata	attactgtaa	atggaacaac	aacaacaata	aaacacacgt	1680
taaacatc						1688

<210> 73  
 <211> 1138  
 <212> DNA  
 <213> Homo sapiens

<400> 73	
ggggcgctgt	agtcccagct attcaggagg ccgaggcagg agaattgcct gaactcagga 60
ggcggaattg	cagtgcgacc agatcgcgcc attgcactcc agcctgggtg acagagtgcg 120
actctttctc	ccaaaaaaaaa aaaaaaaaaa aaagtcaaat gcagctggga atgtggttcg 180
tgcccttttg	tatattaacc atttgaaact tgggtgtaag gtgggggttg caatgtcagg 240
cctggctgca	gcagctcatg tctttagagt gtgcctcttc cctctctcgt ggggctcgag 300
caagactacc	ttcatacatg ggctctccag ttacatagca actccagtgt taaattccat 360
cttttcttcc	tggaagagcc gtagaaagga cacctggaca tgccctgctgc acaggttgtc 420
tgccctcccc	atcagccsca gaaggaggaa ctttgctctc ttctctcaca gctgtgtgtg 480
cataagaagt	agttcggatg atgtgggtcc caccatgtat tccttctctg ttccatgtag 540
agtaaaataa	atgggagttc tgtttaatgc atcacctcgg ttcatattgc atttgccaag 600
aaagtgcatt	tttattgaac attaggattg aattcttaac tgagtaatca atttcagtag 660
taagttaaaa	tgcccttctat taatggacaa ctgcaaccgt taatcagagt tacagtagat 720
taacagttgt	cagcattttat gctaatagca ctaataaacc gtgggctcat gatttgcact 780
ttataattcc	atatttctca aaacagttgg taatactttt tgcttgaagg tattgattct 840
tttgctccct	tgcttgctac ttggagatgt agagaaagct aaatgacatt ttcacggtga 900
tgacacaata	tcaccttctg cttttgcaca cttggctttg tgtcaaaata gatggaaagg 960
gttcatttgt	tctggtgctc tactgtttaa tttgatctgg tgtgtgacta aagcaagaca 1020
aatagtattt	ttaatgaaac catttaataa cctctggtag cttagagtcg aaggcatttg 1080
aaaaatgcaa	ttaaggatg cctagatgta aacaaaaaaaa aaaaaaaagg gcggccgc 1138

<210> 74  
 <211> 777  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (761)  
 <223> n equals a,t,g, or c

<400> 74	
gtagcacctt	gaaattgggc agttctgaat atgctgttga gtaaaggga aatcactatc 60
tttttaggac	ctttggaatg tggctccatg catttgctaa cgttgttctc ttcagggtcg 120
atttttctgg	gctgttctac tcctctatcc ttctgtgatt gtcttccaat tcttttatta 180
tgggttagagt	tccctgtaga aaccagtggt gtgtgtagtt aacaagtgtc aaaaggagta 240
gaataattac	tttatgtgat gtacttacga gaatactact tagtagaatc cagtataacc 300
aaacaaaatg	tagacgtatt taactatcca gtgtgtcagc tacacatttt ctcatcttta 360
tcacttctgc	tctggatatt gtgatctact ttcttatctc tttgtatttg tkttttcaca 420
tttctttttt	gtgtaaactg ctctatactc ttattgaaac ttgagcataa ttttatattt 480

acatagtaaa	gtttctgata	tgattagaac	ataagttgtw	tctcctaatt	ttccaataga	540
gccattgatk	tttcatttta	acccctttta	atggaacact	tactagcttt	ctaaattata	600
aacttactaa	ctttaaatat	acatgaatta	tttctcagca	ttcttaaaac	aagggtactg	660
aacttcgwtt	tcttgatgat	tcaggggaaa	agaattctga	gtgttgga	ggactttaga	720
tgtcttccaa	ggatttatgg	gatcaattta	agaaaaaaa	naaaaaagg	cggccgc	777

<210> 75  
 <211> 1060  
 <212> DNA  
 <213> Homo sapiens

<400> 75						
gatgtatttc	cttaatatgt	agtttcagaa	gtggaattta	ttagagttaa	actaaactca	60
ttaaatttag	agtttcttat	tgtctttcat	gagaacattt	ttccttttca	ttcataaatg	120
atattgaaac	actatattct	tactttcata	ttcctgttta	tatttttggt	tttcatgtta	180
aacattttac	atttctaata	taacctcatc	gacctgttaa	aaggcaatat	aagatttaga	240
ttattaaata	gcatgtaata	tatgtgatca	gtaatcttca	atgagcttgk	tcttcattta	300
attgcaacgt	tatgtctgat	tttttttgkt	gcaaagcttt	cagaatcttg	acttgtggta	360
atcttctttt	aaaaaagctt	ttaacagaat	taatargtca	tcacgttatg	ataaatgatt	420
aaggaaatga	tgcctctaata	acatkgaatt	attaaaacta	tcattttgaa	aaattatatt	480
ggtacaaact	agtggtctact	gctattactc	atacatttca	gaattcatac	atggatatcg	540
tctaggattt	tttttttgcg	taatcatgag	ttacggtggt	aaagttatag	tgtaatttta	600
attatgttat	agtggttaatt	tatctgtttt	acatctcact	tttgatatctg	aaaccgttcg	660
aaaataatta	ttattaaagg	ccagttgaca	aaattttccac	tctcctccc	cagtgtgact	720
ttccttattt	gtattatacc	tataaagact	acctcttaca	tcggccaggc	acagtggctc	780
acgtctgtca	tcccagcact	ttgggaggac	gaggtgggca	gattgcctga	gctcaggagt	840
tggagaccag	cctgggtaata	atagtgagat	cctgtctcta	caaaatatac	aaaattagct	900
aggcgtgcct	gtagtcccag	ctacttgga	ggctgaggtg	gtaggatggc	atagagtcca	960
ggaggcagag	gttgcagtga	gctgagatgg	tgccactgca	ctccagcctc	agtgtcagag	1020
ccagtcctctg	tctcaaaaaa	aaaaaaaaaa	ggcgccgcgc			1060

<210> 76  
 <211> 1503  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (6)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (18)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (41)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE

&lt;222&gt; (1501)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 76

gtggangccg	ctcctganaa	ctagtgggtc	ccccgggctg	ncaggattcg	gcacgagaat	60
gaatggcaaa	gaaatagaag	gggaagaaat	tgaaatagtc	ttagccaagc	caccagacaa	120
gaaaaggaaa	gagcgccaag	ctgctagaca	ggcctccaga	agcactgctg	atgaagatta	180
ttactaccac	cctcctcctc	gcatgccacc	tccaattaga	ggtcgggggtc	gtggtggggg	240
gagaggtgga	tatggctacc	ctccagatta	ctacggctat	gaagattact	atgatgatta	300
ctatggttat	gattatcacg	actatcgtgg	aggctatgaa	gatccctact	acggctatga	360
tgatggctat	gcagtaagag	gaagaggagg	aggaagggga	gggcgagggtg	ctccaccacc	420
accaaggggg	aggggagcac	cacctccaag	aggtagagct	ggctattcac	agaggggggc	480
acctttggga	ccaccaagag	gctctagggg	tggcagaggg	ggcctgctc	aacagcagag	540
aggccgtgg	tcccgtggat	ctcggggcaa	tcgtgggggc	aatgtaggag	gcaagagaaa	600
ggcagatggg	tacaaccagc	ctgattccaa	gcgtcgtcag	ccaacaacca	acagaactgg	660
ggttcccaac	ccatcgctca	gcagccgctt	cagcaagggtg	gtgactattc	tggtaaactat	720
ggttacaata	atgacaacca	ggaattttat	caggatactt	atgggcaaca	gtggaagtag	780
acaagtaagg	gcttgaaaat	gatactggca	agatacgatt	ggctctagat	ctacattctt	840
caaaaaaaaa	aattggctta	actgtttcat	ctttaagtag	cattttgctg	ccatttgtat	900
tgggctgaag	aaatcactat	tgtgtatata	ctcaagtctt	tttatttttc	ctcttttcat	960
aaatgctctt	ggacattatt	gggcttgcag	agttccctta	ttctggggat	tacaatgctt	1020
ttatcgtttc	aggcttcatt	ttagcttcaa	aacaagctgg	gcacactgtt	aaatcatgat	1080
tttgcagaac	ctttgggttt	ggacagtttc	atttttttgg	atttgggata	gattacatag	1140
gagtatggag	tatgctgtaa	ataaaaatac	aagctagtgc	tttgtcttag	tagttttaag	1200
aaattaaagc	aaacaaattt	aagttttctt	gtattgaaaa	taacctatga	ttgtatgttt	1260
tgcatcccta	gaagtagggt	aactgtgttt	ttaaattgtt	ataacttcac	acctttttga	1320
aatctgccct	acaaaatttg	tttggtttaa	acgtcaaaaag	ccgtgacaat	ttgttctttg	1380
atgtgattgt	atttccaatt	tcttgttcat	gtaagatttc	aataaaacta	aaaaatctat	1440
tcaaaacaww	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1500
nna						1503

&lt;210&gt; 77

&lt;211&gt; 872

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (844)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (858)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 77

ggggaagtgc	ttcactgcct	tgcatttgac	tccagatccc	tccatcctcc	cagagccttg	60
gcctcaaaaa	tgctgattct	agcatcatgg	aaatgctgtc	ctcaaagtgg	tctaaacggg	120
ttgctgcttc	acttgctcac	ttaatctccc	ttttcatagg	gctgttggtt	ttacttctgg	180
gaagtctctg	ttaccctgga	acagaaactc	tcttccctaa	aagttgattt	tattgaccga	240
tggaggccag	agacacttag	gcataatttc	cctccagact	agaagcttct	gaggaggacc	300
tcctgagttc	gcaccctggc	tccttgctgt	gctgagggcc	cccgtgttaa	cctcacgttg	360
tgctcctctc	gattcagagg	gcccgagtgt	gttctgtcag	ccaggcagtg	gccccagctc	420

tacagaaatg	agttgtcatt	gcatacctagg	gccaggggtct	tcgtgcttgt	gtgtgtttacg	480
tgggaagtatg	tggacaccaa	gtgttcctgg	atggccacag	cctgcgaagg	aaactggggc	540
cagcagctgc	tctgtgtttt	cagccaacaa	tggctcctgc	ccactgccgc	tgcataacca	600
ccagaggcag	gcttctcttg	acacaggcct	gtcgttggag	catgtgcctg	gcgagtccta	660
tttctattcc	cctgtgggtt	agggacaggc	agctgtacct	tcagtgtgtt	gctggggcag	720
gagaatcgct	tgaaccggga	ggcggaggtt	gcagtgagcc	aaaattgcac	cactgcactg	780
cagtctgcag	gacagagaga	ggctmtatct	caaaaaaaaa	aaaaaaaaaa	actcgagggg	840
gggnccggga	cccaattngc	catataggaa	aa			872

<210> 78  
 <211> 573  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (560)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (563)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (566)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (567)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (571)  
 <223> n equals a,t,g, or c

<400> 78	
gatcaagttc	cttagttttg
attcaacaag	tattttttgt
tcttttgcct	gttaactaat
gagaaacttg	tgtatggtea
atccagtaag	attaccatgg
aattattatt	ttggaatgta
agtcattttc	ttcatgaggt
tcatgcattt	tattgcccct
gtgatattga	tgatcctgac
gctgacaaaa	aaaaaaaaan
	aanaannaaa
	naa
	60
	120
	180
	240
	300
	360
	420
	480
	540
	573

<210> 79  
 <211> 1509

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 79

ggcacgagga	tgtacctaat	gagcttctcc	attcactttg	taaaaataat	ttgtatgtgt	60
accatcttgg	tcctctcccc	tcccgttttg	ttaaaatata	aggatagcac	tcccaggcca	120
cttttggtctc	agtgtgaagat	ccctattaac	tatctgaaag	gaaaatagag	ccaagacctc	180
tgggtctcaaa	tatataggaa	ttgcctttct	ttagtcttca	ggactattgt	gtgaaaacaa	240
gtaggggtct	aatctcctag	aaggtagggg	ctttatcctt	aaagagaata	tgtccccaga	300
ttattagcac	tttttagagga	gaagccaagg	tatgtagggg	tgtgtggctg	gcccacagtc	360
ggagcacgaa	gagagaatgg	gataccattg	tgggaagaga	agaaaagttc	ctcagggggc	420
tcccactgct	aaagtttttt	gtgagatggt	gatctgtgct	tcttgatttt	gactttttaa	480
ggaattatct	tggcagcaca	tgtagtattc	ttggatgata	ttgctgctct	tatttctcct	540
tttgtgtgtg	tgtgtgtgtg	tgtgtggcta	tgggttttca	tttgtaactc	catctgctta	600
ggagagtggg	ctctctataa	gggaacctgc	tgtaaacttc	attgcagcaa	ggatgtagag	660
agaaaatagga	cttaattcca	ctaggggctc	tcactctaca	ccttaaggag	gagatttcta	720
gaaaaactgg	gccagatttt	ctttgttctc	catcatttta	atgtggcagg	ctgttcagtt	780
ttcttactct	tacctatgtg	atatttcttc	gtaacgtgtc	caaaaagaaa	aaagacccaa	840
tcagtgtctc	ttgactttgt	tctttgatcc	ctcagtttct	tcttgatttc	agcatgtgtc	900
gggttcctaa	ttttgggtat	gagttagcaa	atttaaccat	tgtgtttgtg	ccctaccag	960
gggactcccc	agtttctgac	ttgaagtaga	ctgagaagaa	tccacgaggt	gctatctggc	1020
cagatttaag	tagattctat	ttccttgggt	ctccctctcc	ctgaggacct	cttattttat	1080
tgtccctctc	tctaggttaa	ttctcctttg	atttgacttt	gttgagaagg	aggttggaca	1140
gtagatttagc	taactttcaa	gtgcaaaatt	acagtgtgtg	agagtgtggg	gggaaaatta	1200
gtcttatttt	ttcctacatg	ggatacaaca	ctgtgaattc	aatcttcaac	tgaaggccct	1260
gcagttctcc	taaaacatag	ttgtttgttt	ttctttaaca	aagtttaagc	tagtggtaat	1320
aaattaaaaa	aaattgcttg	tctgtctact	tcagctttgt	tttatgcccc	tttcatattg	1380
ttgtctgtgt	tgtaattcat	aacttttgat	accatttctg	atgtgtaaaa	ttgggtgtct	1440
tgtaaatatc	ttataaagag	ttcaattgta	aataaactat	tgtggctgtt	aaaaaaaaaa	1500
aaaaaaaaaa						1509

&lt;210&gt; 80

&lt;211&gt; 1109

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 80

ccacgcgtcc	ggccgcagaa	cgggctccgc	ggacgacggg	ctccagggac	gcacaggcag	60
cgggacctccc	accgcgggtg	ccgggggcgg	gggggctgcc	cccatgcggg	gcccttcctg	120
gtcgcggcct	cggccgctgc	tgtgtgtgtt	gctgtgtgtg	tgccttggc	ctgtctgggc	180
ccaagtgtcg	gccagggcct	cgccctcggg	gtccctgggc	gccccggact	gccccgaggt	240
gtgcacgtgc	gtgccgggag	gcctgccagc	tgtcggcact	ctcgtgccc	gccgtgccc	300
cgggcctgag	cctgcgcctg	cgcgcgctgc	tgtggacca	caaccgcgtc	cgtgcgtgc	360
cgccaggtgc	cttcgcggga	gcgggcgcgc	tacagcgctt	ggacctgcgc	gagaacgggc	420
tgcactcggt	gcatgtgcga	gccttctggg	gcctgggcgc	gctgcagctg	ctggacctga	480
gcgccaaacca	gctggaagca	ctggcaccag	ggactttcgc	gccgctgcgc	gcgctgcgca	540
acctctcatt	ggccggcaac	cggctggcgc	gcctggagcc	cgcggcgcta	ggcgcgctcc	600
cgtgtctgcg	ctcactcagc	ctgcaggaca	acgagctggc	ggcactcgcg	ccggggctgc	660
tgggcgcgct	gcccgtctta	gacgcgctgc	acctgcgcgg	caacccttgg	ggctgcgggt	720
gcgcgctgcg	cccgtctctg	gcctggctgc	gccggcaccc	gctgcccgcg	tcagaggccg	780
agacgggtgct	ctgcgtgtgg	ccgggacgcc	tgacgctcag	ccccctgact	gccttttccg	840
acgccgcctt	tagccattgc	gcgcagccgc	tcgccctgcg	ggacctggcc	cgtgggttac	900
acgctcgggc	cggcctcctt	cctcgtcagc	ctggcttctt	gcctggcgct	gggctctggg	960
ctcaccgcct	gccgtgcgcg	cgcgcgcgc	ctccgcaccc	cgcctctccg	cccgcgcgga	1020



ccgtccagac	ccgaaccccg	atccccgaccc	ccacggctgt	gcctcgcccg	cggacccggg	1080
gagccccgtc	cgctgccgcc	caagcctga				1109

<210> 81  
 <211> 807  
 <212> DNA  
 <213> Homo sapiens

<400> 81						
cccacgcgtc	cggacgtcct	gatagatcct	ctgctccaat	aggcaactcc	ggccttcctt	60
gccctgacct	ggaacctctg	ggagggctgc	agagtaagtg	ccgcctctgc	gctccgacgg	120
aggcacgagg	cctgtggagt	aggtccctct	gttccgacag	gtgcgacact	tggcgctcca	180
tgcttgccgg	tgccgggagg	cctggcctcc	cccagggccg	ccacctctgc	tggttgctct	240
gtgctttcac	cttaaagctc	tgccaagcag	aggctcccg	gcaggaagag	aagctgtcag	300
caagcacctc	aaatttgcca	tgctggctgg	tggaagagtt	tgtggtagca	gaagagtgtt	360
ctccatgctc	taatttcggg	gctaaaacta	cccctgagt	tggtcccaca	ggatatgtag	420
agaaaatcac	atgcagctca	tctaagagaa	atgagttcaa	aagctgccgg	ttcagctttg	480
aatggaacaa	cgcttatttt	ggaagttcga	aaggggctgt	cgtgtgtgtg	gccctgatct	540
tcgcttgtct	tgctatcatt	cgtcagcgac	aattggacag	aaaggctctg	gaaaaggctc	600
ggaagcaaat	cgagtccata	tagctacatt	ccacccttgt	atcctgggtc	ttagagacct	660
tatctcagac	agtgaagtgt	aaatggactg	atgtgcactc	ttggttcttt	ggagccttgt	720
ggtggaatcc	ccttttcccc	atcttcttct	ttcagatcat	taatgagcag	aataaaaaga	780
gtaaaatggt	aaaaaaaaaa	aaaaaaa				807

<210> 82  
 <211> 1043  
 <212> DNA  
 <213> Homo sapiens

<400> 82						
ggcacgagtt	gggccgggca	cccccagaag	ctgaccttga	gacaaggatt	tgggtgcaag	60
tggtttattt	ggcaggtgcc	cagaaagtgc	tgacaggagt	gggaaagtga	gttaggggag	120
agaaggaagc	cactacaggc	tatgttcatg	tgcaggttac	tgctgtgggc	aactggggct	180
tacggatttc	taggagatga	cgtggaatac	acctcagtg	tgccccacca	gaagggaag	240
gaagcatggg	tatttatatg	tcagctccca	ttcattattg	gctgagggca	gtcctagag	300
ggcattgggt	ctgcgtttca	agcctgctgc	acataggctg	agaggaatcc	ctgagttcga	360
gtcacaggcg	cccacagtca	tgctcagaca	gcacatacag	gaacagtgtg	tgaggggggc	420
ataggtggga	cacaaatacc	accagttata	aagaggaaag	atgggaagga	aagacaagag	480
gaaggtgtgg	agtttagattc	ctgggtcaga	tgtgaacccc	tggtctctca	aacactcctt	540
ctttttttct	ttttcttttt	ttttgagaca	ggatctcact	ctgttgacac	ggctagagtt	600
cagtgggtgt	atcaggggtc	gtggcagcct	ctacctccta	ggctcacatg	atcctccac	660
ctcagcctcc	tgagttagctg	ggactagagg	cacacatcac	cacacttggc	tagtatttaa	720
atttttctgt	agaagtccag	gcgcagtggc	tcatgcctgt	aatcccagca	ctttgggagg	780
ccgaggcagg	tggatcacct	gaggtcagga	gttcaagacc	agcctggcca	acatgggtgaa	840
accccgccct	tactaaaaat	acaaaaaaat	tagcctgggtg	tcgtggcagg	ctcctgtaat	900
cctggctcct	tgggaggctg	aggtaggaga	atcacttgta	cccagaatgt	ggagcttgca	960
gtgagctgag	atcatgccat	tacactccag	cctgggcaag	aagagtgaag	ctccatcgca	1020
aaacaaaaaa	aaaaaaaaaa	aaa				1043

<210> 83  
 <211> 1173  
 <212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (548)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (603)

<223> n equals a,t,g, or c

<400> 83

gctgtctcag	aaaaaagaaa	aaagtttcta	aagtaaaaat	tgaaagtact	tcccctacaa	60
ccacagggttg	ctttgacaga	ttaatgtaaa	ttcttccaga	tactcttctg	tggatgtaga	120
aacatgcaga	atgaggcaag	ctttaatttg	cttatgtcac	ttactgtgga	tagcctttca	180
tatcttataa	gttaatgtca	gagcagcaat	ctcatttttt	tccaatttgt	aaacatttta	240
tttaacctta	tgatggatat	tttgggtgat	ttcagtatta	caaaaatgcc	tattaatagt	300
atattttcat	tatatctctg	ttacgaaatt	ataatgctac	aaacattact	atgcctgtgg	360
cagtatacat	ctgcacaagt	tttgaaaatg	ttatgcattc	ataggcaaaa	atgggataac	420
ttttgggcag	tggtcatgat	taatctgttg	atcagaatcc	agagattgcc	cttctccttg	480
ccaattgctt	taagagtacm	ctagtttttg	gccgggtgca	rtggctcatg	cctgtatccc	540
agcatttngg	aggccaagac	gggcgggatca	caagggtcagg	agatcgggac	catcctggct	600
aanttggtga	ggccccattc	tactaaaaat	tccaaaaaaa	cccacmaaaa	ccaaaaaac	660
ccrgccttgk	tggtgggatt	acaggcatgt	gmacaacaac	ccggctaatt	ttttttgtat	720
ttttagtaga	ggtgggggtg	caccatgttg	gccaggctga	tctcaaactc	ctggccttaa	780
gtgatctgcc	cacctcggac	tcccaaagtg	cggaattaca	ggcgtgagcc	accgcgcccg	840
gccactgggt	tttaaacttt	attttgaaat	tatttcaggc	tgggcgcagt	ggttcacgcc	900
tgtgatccca	acactttggg	aggccgaggc	gggcgggatca	cgagggtcagg	agatcaagac	960
catcctggct	aaccccgctc	ctactaaaaa	tataaaaaat	cagccgggca	cgggtggcagg	1020
tgctgttagt	cccagctact	cagtgggctg	aggcaggaga	atggtatgaa	cccgggaggc	1080
ggagcttgca	gtgagctgag	atcacgccac	tgcactccag	cctgggagac	agagtgagac	1140
tctgtctcaa	aaaaaaaaaa	aaaaaaaaactc	gag			1173

<210> 84

<211> 1561

<212> DNA

<213> Homo sapiens

<400> 84

ggcacgagtg	aggctcatgt	ctgacctgca	gaactgtata	atgataaatt	atgttgtttg	60
aaaccgctac	atttgcggtg	atttgttaca	gcagcaatag	aaaacgaatc	ccctgcccag	120
aatgacttcc	tccttttctg	tgggacgaag	gtcaggcct	tctgctgaaa	gcttgctccc	180
ctaagtagtc	acaccaatg	ccgaatactc	cccagaagca	gctgctatth	tctgaggaca	240
atgagttgct	tgtaagcctg	agaacaggac	gaaaaccac	tttgcaagca	gccctgcgtg	300
tgacgggcat	gccctcggag	ggcagggttg	ttttgctatc	tgctttctgt	cctgcctttt	360
tccccccatg	ggctcctgtc	ggctcttttg	ctttctcact	ttgtgcagaa	agccatctca	420
actcttctca	caggagaata	gctgtatgga	cgtagcaggg	ggagttacca	catgcctacc	480
tccatggttt	tcgagagggg	cccctgccc	aatgtctcag	tggccacctt	catcagacca	540
tggagcagtc	agagcgggaa	gggattctag	agttgggtcca	gtccaacat	ctcatcttac	600
atgtgaagga	ggaaaggaag	aaagggagaa	aaataagaaa	gctgaggtca	accctcctac	660
agggatgggc	ctggccaaca	ggatcccaag	ggatgacata	acattgaaat	taagaaacca	720
aggaaagttg	agaactaaag	aaaacagaac	ccagtcagcc	aagaggcatc	cttgaggggc	780
aaccaagccg	tcaaacctgg	atgcccccca	cgagtcagaa	agtcgggtgc	ctcaagagcc	840

aagcagccaa	gaaatggggt	ctggaaactgg	cacttttggtc	cgctctgtg	cactcaccca	900
gaaagggtg	aagggaacct	gggaccaagt	gccaagggtca	cacaacggat	gaatagactg	960
ctggacttca	aactgaacat	gccattttgc	caaagcagtc	atcaccttcc	gtgaatcata	1020
aatgtttgtt	caaagccaca	aatgtatata	ctctttgtat	gtatacagat	tttttctaaa	1080
ggttaacatc	taaacagatc	aattaagggtc	agccttaatt	tgtctgagct	ttttgggttaa	1140
agtttcctga	gtaattgagc	gaattcaagt	ttctggcttt	ctcctttctc	tttctccatt	1200
taaaacatga	tctcatgaaa	tttttgtccc	aagaaaggca	ggattacatt	ttcttttaac	1260
agtttgagtt	ggtgtagtgt	attcttggtt	atcagaatac	tcatatagct	ttgggatttt	1320
gaattggtaa	atattcatga	tgtgtgaaaa	atcatgatac	atactgtaca	atctcagtgc	1380
cacaaaattg	gatgttgtgc	ctacacacgc	acaggaccta	gaagagcatg	tcaaaactata	1440
aactgcctgt	gattgtgaat	gactttgttc	tttgcttctt	gcgtttttca	gtttcctata	1500
atgcacatct	taacttttaa	aaaataaagg	ttatttttaa	agccaaaaaa	aaaaaaaaaa	1560
a						1561

&lt;210&gt; 85

&lt;211&gt; 1433

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 85

cccggagccg	tggacgccct	acagctgaga	aggggaccca	aggggtcggc	cgcgcccaag	60
gcccctagga	cgccgcgcc	agctcacgct	gccgacggca	ttatkagaca	ttctgcgtca	120
ggtccgggct	cctggacttc	gcctttcccg	agccctggag	gtggggagaa	aaggttcacc	180
aatttttaaa	atccaaatat	atctcatggt	acagtggaa	aactggccag	agagtctgga	240
agtttggtt	ctggctctgg	ctgtgccact	gactcactgt	gaccttgga	tcttgtgtg	300
tgaagacatt	tcccaagtgc	ttcatgttag	ccagcaaata	tgaccacaaa	ggcctggaaa	360
gaggtgattg	ttaggttgcg	cagaggtggt	cttatccagc	tcagcttccc	ctgggaccca	420
ccgtgggacc	tgaggcagaa	ctgggggtgga	cttggcctcc	tccatggcac	accggctgca	480
gatacgactg	ctgacgtggg	atgtgaagga	cacgctgctc	aggctccgcc	acccttagg	540
ggaggcctat	gccaccaagg	cccggggcca	tgggctggag	gtggagccct	cagccctgga	600
acaaggcttc	aggcaggcat	acagggctca	gagccacagc	ttccccaact	acggcctgag	660
ccacggccta	acctcccgc	agtgggtggc	ggatgtggtc	ctgcagacct	tccacctggc	720
gggtgtccag	gatgctcagg	ctgtagcccc	catcgctgaa	cagctttata	aagacttcag	780
ccaccctgc	acctggcagg	tgttggatgg	ggctgaggac	acctgaggg	agtgccgcac	840
acgggggtctg	agactggcag	tgatctccaa	ctttgaccga	cggctagagg	gcatectggr	900
gggccttggtc	ctgcgtgaac	acttcgactt	tgtgctgacc	tccgaggctg	ctggctggcc	960
caagccggac	ccccgcattt	tccaggaggg	cttgcggctt	gctcatatgg	aaccagtagt	1020
ggcagcccat	gttggggata	attacctctg	cgattaccag	gggcctcggg	ctgtgggcat	1080
gcacagcttc	ctggtgggtt	gcccacaggg	actggacccc	gtggctcagg	attctgtacc	1140
taaagaacac	atcctcccc	ctctggccca	tctctgcct	gcccttgact	gcctagaggg	1200
ctcaactcca	gggcttttag	gccagtggag	gaagtggctg	gccctaggcc	atggagaaaa	1260
ccttaaacaa	accctggaga	cagggagccc	cttctttctc	cacagctctg	gacctttccc	1320
cctctctctgc	ggcctttgtc	acctactgtg	ataataaagc	agtgagtgtg	gagctctcac	1380
ccttccccca	ctaaaaaaaa	aaaaaaaaaa	actcgagggg	gggcccggta	ccc	1433

&lt;210&gt; 86

&lt;211&gt; 1377

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 86

ggcagcaggt	ccagtcctga	ttccatcttc	ttacaagtta	gggagctggg	tccaggcctg	60
gatccatggt	attatgaatc	aggaagttgg	gtccaggcct	ggctccatgt	tcctgcagg	120

cagggcaggt	cttccccga	gtgatggctc	ttggactgtg	ctcctctggg	gccctctcaa	180
ctctgtgtct	gtcatctgtc	acctgcctgg	ccattatggg	tttgatggca	gtggatgggc	240
tccatgggac	ttcaggcctg	gggtgagact	caggaccctg	gggtgggcat	ggatggggat	300
attggacccc	tgaagaagg	gaagctgaga	gacttttttc	ctttaaagac	ttttccatgt	360
tatctccact	cagagaattc	ttttctgcaa	agtcacggga	gggaggtgac	attgagccct	420
ccaatgtgac	agaaactgtg	ctgggaactt	tacatgtgtt	acctaatttg	tttaattatc	480
ccagcaactc	cacaaagtag	gcatttttat	tgttgaggaa	acagaagctt	agagactttg	540
tgagacttgc	ccgagacccc	aggtcacaca	ccagcaagga	tgaggtcaag	cttttaatcc	600
aggtctgect	ggctccaagt	ccacaccctt	tcacaacaat	gaactttctt	tatgattgca	660
gatattattt	ggggaacttt	acatcaaaca	ttgactacat	aaaacttcaa	ccatagacta	720
tattctttgt	tttggaact	gtgaagactc	aaatttttta	taaactcaga	acagcttcca	780
gttttctcta	gatatcggaa	gatgggctgt	gttttttgtc	tgttgtccag	tgaggtgat	840
ttgtagtcag	acaggtgagt	cagtttggtt	ggagtaggct	attgtggttc	tctctcatca	900
ggaaagaggg	gatgcacttg	gcccccaac	tccaagttgg	tgggtgcgatg	atttttccat	960
attctccctt	aacaggctgt	gagggagtct	gggccaggca	ctaggccatg	agcagggcag	1020
actggggtaa	acccttagcg	agcctctctc	cagccacgag	gaaacctgga	gtgtgtgctg	1080
gectgtgtgc	tgtgtgtgtg	tgtgtgtgaa	tgcacacgtg	tgtgcatgca	ctgtgagctg	1140
gtgtgtgcat	gtgactgggt	gtgtgcgttt	gtgtgtgtgt	gtgtgtgtgc	atgtgtgtgc	1200
tgggtgcaca	catgcatatg	tctctgtgta	tacatgtgta	tgtgtgccag	tgggtgcag	1260
tgtttgtaca	gtgtgcgtgt	gtgtgtgtgt	ttgtgcacat	gagctgctgc	acacataata	1320
gccttgtgaa	ttaggggaag	aagaaaggct	ccggcttaca	aaaaaaaaa	aaaaaaa	1377

&lt;210&gt; 87

&lt;211&gt; 1715

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 87

ggcacgaggg	acattggagc	tccccacacc	actcattgct	gcccaccagc	tatacaacta	60
cgtggctgat	cacgccagct	cttaccacat	gaagccattg	cgaatggccc	ggccaggggg	120
cccagaacac	aacgagtatg	ccttgggtgc	ggcatggcac	agttctggct	cctacctgga	180
ctctgagggg	cttcgacacc	aggatgactt	tgatgtgtct	ctgcttgtct	gtcactgtgc	240
tgcacccttt	gaggagcaag	gagaggctga	gcggcacgtt	ctgcggctac	agttcttctg	300
ggtgctcacc	agccagcgag	agctcttccc	caggtcact	gctgacatgc	gccgcttccg	360
gaagccaccc	agactgcccc	ctgagccaga	ggctcctggg	agttcagctg	gcagccctgg	420
ggaggccctca	gggcttatct	tagcgccctg	accggctcct	ctgttcccac	cactggctgc	480
agaggtgggc	atggcacgag	cacggctggc	tcagctgggtg	cggctggctg	gagggcactg	540
ccgtcggggac	accctttgga	agcgctctt	cttgcctggg	ccaccggggc	ctgatcgact	600
gcggctaggg	gggcgcctgg	ccctggcaga	gctggaggaa	ctcctagaag	cagtccatgc	660
caaattccatt	ggggacatcg	acccccagct	ggactgcttc	ctatccatga	cggctctcctg	720
gtaccagagc	ctgatcaaag	ttctcctaag	ccgcttcccc	agagctgtcg	ccatttccaa	780
agcccagact	tgggaactca	gtacctgggt	gcgctgaatc	agaagttcac	tgactgtctct	840
gcgctagtgt	tctggactcc	acttaggaaa	gacgtctctg	aagtggtttt	ccgagaagcc	900
cttccagtac	agccccagga	cacgagaagc	ccccctgcc	aactggctct	cacctaccac	960
cacctggagt	ctgtcatcaa	cacagcctgt	ttcacctctc	tggaccgcgc	tcctctgaag	1020
ggagtggact	ggaccactga	atgtcactgt	tccttgaatc	atgggcctac	cagattgcct	1080
gccagaggca	ggactgacca	gcccttcttg	gccccagggc	aagccagaca	ctgagtgaca	1140
ccaaaggctt	tgtaaactatg	tcttgagggt	ctgctgcccc	agcctggcag	caggaaccgc	1200
cctccccaaa	caccacagc	cactgacca	tccaggactc	cagagagtca	ggtcaacccc	1260
gaggaccctt	tgggccttct	tgggggtactc	ctttcgggcc	ccctggtaga	gtctcgggag	1320
ttcacacagg	gtggcaaaca	ccccctagag	ctcctctgcc	tgaatcctgc	cccctagcct	1380
ttgaccactg	tcagccacct	gtgtcccttg	agccttcggg	tcttcaactc	ccacttggac	1440
atcactgctg	gacattccca	tcgagatgac	acctgggttc	caatcccagc	tctgcctttg	1500
aagcacttgc	ggccaccgtc	aagtcctttt	gctctcggac	cctgggtttc	tcattcctta	1560

atgagggtggg	ttcagaagct	ctcccatctt	cacagcaacc	ctggcactgg	cttctcaatg	1620
ggaggggaagt	cagcagagaa	actgaagtgt	tagacactat	gtgtcccacc	accccattac	1680
agagacatat	gacaatgaaa	aaaaaaaaaa	aaaaa			1715

&lt;210&gt; 88

&lt;211&gt; 417

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 88

ccacgcgtcc	gctcctctag	aggetccaca	tgaagtccca	gtgctacagt	cctagttatt	60
ttgccttctt	ctgcctgggt	ttctttcaga	tcacctcagc	cagttctcag	acacttaggg	120
gacatgttct	ctgcaggacc	actctgaggg	actcttctgc	atattgctga	cctgagagga	180
tggcctcaga	gctgacttgg	gcaatcctcc	ccaacaggaa	ggggagacat	tgcctgccac	240
tgaggaaaca	ggatcatgaag	gtggagataa	gctgcaaggg	gcgaagcaac	tttatgtcag	300
tggaaaacgt	gtctctttta	agctgctatg	tgaacagctt	ttacagtcac	taaatttacc	360
taaactaagg	ttaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaa	417

&lt;210&gt; 89

&lt;211&gt; 1167

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (432)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 89

gggggtgggg	caggcgacgg	tggggaagat	ggcgtaccag	agcttgcggc	tggagtacct	60
gcagatccca	ccggctcagc	gcgcctacac	cactgcctgc	gtcctcacca	ccgccgccgt	120
gcagttggaa	ttgatcacac	cttttcagtt	gtacttcaat	cctgaattaa	tctttaaaca	180
ctttcaata	tggagattaa	tcaccaactt	cttatttttt	gggccagttg	gattcaattt	240
tttatttaac	atgatttttc	tatatcgta	ctgtcgaatg	ctagaagaag	gctctttccg	300
aggctcgaca	gcagactttg	tatttatgtt	cctttttggg	ggattcttaa	tgaccctttt	360
tggctctgtt	gtgagcttag	ttttcttggg	ccaggccttt	acaataatgc	tcgtctatgt	420
gtggagccga	angaaccctt	atgtccgcat	gaacttcttc	ggccttctca	acttccaggc	480
cccctttctg	ccctgggtgc	tcattgggatt	ttccttgggt	ttgggggaact	caatcattgt	540
ggaccctttt	ggtattgcag	ttggacacat	atattttttc	ttggaagatg	tatttcccaa	600
tcaacctggg	ggaataagaa	ttctgaaaac	accatctatt	ttgaaagcta	tttttgatac	660
accagatgag	gatccaaatt	acaatccact	acctgaggaa	cggccaggag	gcttcgcctg	720
gggtgagggc	cagcggtctg	gaggttaaag	cagcagtgcc	aataatgaga	cccagctggg	780
aaggactcgg	tgatacccac	tgggatcttt	tatcctttgt	tgcaaaagtg	tggacacttt	840
tgacagcttg	gcagatttta	actccagaag	cactttatga	aatggtacac	tgactaatcc	900
agaagacatt	tccaacagtt	tgccagtggg	tcctcactac	actggtactg	aaagtgtaat	960
ttcttagagc	caraaaactg	gagaaacaaa	tatcctgcc	cctctaacia	gtacatgagt	1020
acttgatttt	tatggtataa	gcagagcctt	ttcttctctt	tcttgataga	tgaggccatg	1080
gtgtaaatgg	aagtttcaga	gaggacaaaa	taaaacggaa	ttccattttt	ctctcactgt	1140
aaaaaaaaaa	aaaaaaaggg	cggccgcg				1167

&lt;210&gt; 90

&lt;211&gt; 1892

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 90

ccacgcgtcc	gcgggaccgg	acggatcttc	tccggccatg	aggaagccag	ccgctggctt	60
ccttcctca	ctcctgaagg	tgctgtcct	gcctctggca	cctgccgcag	cccaggattc	120
gactcaggcc	tccactccag	gcagccctct	ctctcctacc	gaatacgaac	gcttcttcgc	180
actgctgact	ccaacctgga	aggcagagac	tacctgccgt	ctccgtgcaa	cccacggctg	240
ccggaatccc	acactcgtcc	agctggacca	atatgaaaac	cacggcttag	tgcccgatgg	300
tgctgtctgc	tccaacctcc	cttatgcctc	ctggtttgag	tctttctgcc	agttcactca	360
ctaccgttgc	tccaaccacg	tctactatgc	caagagagtc	ctgtgttccc	agccagtctc	420
tattctctca	cctaaccactc	tcaaggagat	agaagcttca	gctgaagtct	caccaccac	480
gatgacctcc	cccatctcac	cccacttcac	agtgcacaga	cgccagacct	tccagccctg	540
gcctgagagg	ctcagcaaca	acgtggaaga	gtcctacaa	tcctccttgt	ccctgggaag	600
ccaggagcaa	gcgccagagc	acaagcagga	gcaaggagtg	gagcacaggc	aggagccgac	660
acaagaacac	aagcaggaag	aggggcagaa	acaggaagag	caagaagagg	aacaggaaga	720
ggagggaaa	caggaagaag	gacaggggac	taaggaggga	cgggaggctg	tgtctcagct	780
gcagacagac	tcagagccca	agtttcactc	tgaatctcta	tcttctaacc	cttctctttt	840
tgctccccgg	gtacgagaag	tagagtctac	tcctatgata	atggagaaca	tccaggagct	900
cattcgatca	gcccaggaaa	tagatgaaat	gaatgaaata	tatgatgaga	actcctactg	960
gagaaaccaa	aaccttgga	gcctcctgca	gctgccccac	acagagcctt	gctgggtgctg	1020
tgctattcga	tcgtggagaa	tacctgcctc	ataaccccc	cagccaaggc	ctggaagtac	1080
atggaggagg	agatccttgg	tttcgggaag	tcggctctgtg	acagccttgg	gcggcgacac	1140
atgtctacct	gtgccctctg	tgacttctgc	tccttgaagc	tggagcagtg	ccactcagag	1200
gccagcctgc	agcggcaaca	atgcgacacc	tcccacaaga	ctccctttgc	agcccttgc	1260
ttgcctccca	gagcctgtcc	atcggcaacc	aggtagggtc	cccagaatca	ggccgctttt	1320
acgggctgga	tttgtacggt	gggctccaca	tggacttctg	gtgtgcccgg	cttgccacga	1380
aaggctgtga	agatgtccga	gtctctgggt	ggctccagac	tgagttcctt	agcttccagg	1440
atggggattc	cctaccaaga	tttgtgacac	agactataat	cagtacccaa	actactgttc	1500
cttcaaaagc	cagcagtgct	tgatgagaaa	ccgcaatcgg	aagggtgtcc	gcatgagatg	1560
tctgcagaat	gagacttaca	gtgcgctgag	ccctggcaaa	agtggaggacg	ttgtgcttcg	1620
atggagccag	gagttcagca	ccttgactct	aggccagttc	ggatgagctg	gcgtctattc	1680
tgcccacacc	ccagcccaac	ctgcccacgt	tctctattgt	tttgagaccc	cattgctttc	1740
aggctgcccc	ttctgggtct	gttactcggc	ccctactcac	atttccttgg	gttggagcaa	1800
cagtcccaga	gagggccatg	gtgggagtg	gccctcctta	aaagatgact	ttacataaaa	1860
tggtgatctt	caaaaaaaaa	aaaaaaaaaa	aa			1892

&lt;210&gt; 91

&lt;211&gt; 523

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 91

cacagcaaag	caagttctaa	gagccaagct	tcagaccaat	ccccaccgt	gaagtcccc	60
gtgcgagtg	cccttgaagg	aggttttcta	acagggtgagt	ggtctgattc	tgtctctgtc	120
ctgtgggatg	gatgggctgg	cacttgatgg	ctctccttcc	ccctcaccy	ccacggagaa	180
ggctggaagg	tgcatttctc	agacttctct	gcctgggaaa	tgggaagtga	tgacagaggat	240
cccaacgtct	cctcggcagg	cttgggtggtg	gacgtgctgg	gccatgttcc	agggggccagc	300
tgctggctcc	gtgggtgctg	agaggaaggg	ggaaggctgt	ctattttttg	gccaggatga	360
atccagcaga	tgtggtaggt	cctggccgct	tgctgacccg	tgggtctacc	gggtgctccg	420
gagctaattg	tccccagatg	ctccaccgtc	ctgatgtggc	agaggcatgg	cattttggcg	480
ggccagtttg	gtggcatcct	gggaaccgtt	ttggaggctc	gag		523

<210> 92  
 <211> 1382  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (1382)  
 <223> n equals a,t,g, or c

<400> 92  
 gccggctggc agcacgactc gcgtagccgt gcgccgattg cctctcggcc tgggcaatgg 60  
 tcccggctgc cggctcgacga ccgccccgcg tcatgcggct cctcggtctgg tggcaagtat 120  
 tgctgtgggt gctgggactt cccgtccgcg gcgtggaggt tgcagaggaa agtggctcgt 180  
 tatggtcaga ggagcagcct gctcaccctc tccaggtggg ggctgtgtac ctgggtgagg 240  
 aggagctcct gcatgacccg atggggccagg acagggcagc agaagaggcc aatgcgggtgc 300  
 tggggctgga cacccaaggc gatcacatgg tgatgctgtc tgtgattcct ggggaagctg 360  
 aggacaaagt gagttcagag cctagcggcg tcacctgtgg tgctggagga gcggaggact 420  
 caaggtgcaa cgtccgagag agccttttct ctctggatgg cgctggagca cacttcctctg 480  
 acagagaaga ggagtattac acagagccag aagtggcgga atctgacgca gccccgacag 540  
 aggactccaa taacactgaa agtctgaaat ccccaaaggt gaactgtgag gagagaaaca 600  
 ttacaggatt agaaaatttc actctgaaaa ttttaaatat gtcacaggac cttatggatt 660  
 ttctgaacct aaacggtagt gactgtactc tagtcctgtt ttacaccccg tgggtgccgt 720  
 tttctgccag tttggccct cactttaact ctctgccccg ggcatttcca gctcttctact 780  
 ttttggcact ggatgcatct cagcacagca gcctttctac caggtttggc accgtagctg 840  
 ttcctaatat ttattattt caaggagcta aaccaatggc cagatttaat catacagatc 900  
 gaacactgga aacactgaaa atcttcattt ttaatcagac aggtatagaa gccaaagaaga 960  
 atgtgggtgg aactcaagcc gaccaaatag gccctcttcc cagcactttg ataaaaagtg 1020  
 tggactgggt gcttgatttt tcttatttct ttttaattag ttttattatg tatgctacca 1080  
 ttcgaactga gagtattcgg tggctaattc caggacaaga gcaggaacat gtggagtagt 1140  
 gatggtctga aagaagttgg aaagaggaac ttcaatcctt cgtttcagaa attagtgtcta 1200  
 cagtttcata cattttctcc agtgacgtgt tgacttgaaa cttcaggcag attaaaagaa 1260  
 tcatttggtg aacaactgaa tgtataaaaa aattataaac tgggtgtttta actagtattg 1320  
 caataagcaa atgcaaaaat attcaataga aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1380  
 an 1382

<210> 93  
 <211> 1747  
 <212> DNA  
 <213> Homo sapiens

<400> 93  
 ccacgcgtcc ggctacctgt gcatcgtgct gctcatgctg ctgctgctca tcttctggat 60  
 cgcgccggcc catggggcca ccaacatcat ggtctacatc agcatctgct ccttgctggg 120  
 cagtttcacc gtgccttcca ccaagggcat cgggctggcg gcccaagaca tcttgcataa 180  
 caaccgcgtc agtcagagag cctctgcct gtgcctggta ctctggccg tgctcggctg 240  
 cagcatcatc gtccagttca ggtacatcaa caaggcgtg gagtgcttcg actcctcggt 300  
 gttcggggcc atctactacg tcgtgtttac cacgctggtc ctgctggcct cagccatcct 360  
 cttccgggag tggagcaacg tgggcctggt ggacttcttg gggatggcct gtggattcac 420  
 gaccgtctcc gtggggattg tctttataca ggtgttcaaa gagttcaatt tcaaccttg 480  
 ggagatgaac aaatctaata tgaaaacaga ctagattgca ataggagctt ggatgggttcg 540  
 aggaataggc attggagggtg gtttctggcc gtgattggat gtgaagtaga agaggtcctc 600  
 gatcatggtg ttagaattga ctggatagta acaggtggtc tgggtggatag cggggagcat 660  
 ggctcagcac cagagcagag gcccgagcag ctctgcagcc caaacgtccc aacggtgcct 720

ggaccatctc	ttctgatgag	acgaatctca	ttttcatttc	cattaacctg	gaagctttca	780
tgaatatttc	ttctttaaaa	cattttaaca	ttatttaaac	agaaaaagat	gggctctttc	840
tgggtagggtg	gtacatgata	gcagagatat	ttttacttag	attacttttg	gaatgagaga	900
ttgtgtcttg	aactctgcac	tgtacaggat	gtgtctgtag	ttgtgttagt	ttgcattaag	960
catgtataca	ttcaagtatg	tcattccaaat	aagaggcata	tcattgaatt	gtttttaatc	1020
ctctgacaag	ttgactcttc	gacccccacc	cccacccaag	acattttaat	agtaaataga	1080
gagagagaga	agagttaatg	aacatgaggt	agtgttccac	tggcaggatg	acttttcaat	1140
agctcaaate	aatttcagtg	cctttatcac	ttgaattatt	aacttaattt	gactcttaat	1200
gtgtatatgt	tcttagatta	gaataatgca	acttcgagta	tgctttaata	tttcaatatt	1260
caagttacaa	atgtataagg	cagttagaaa	taatacagtc	acatgtcact	taatgatagg	1320
gaaacattct	gagaaatgca	ttgtaagggt	actttattgt	gtgaacatca	tggagtgcac	1380
ttatacaaac	ctagatggga	cacctatgac	ccaccacaggc	cagatggtac	agcctgttgc	1440
tcctggggcca	cacacctgta	cagcatgtga	ctgcactgaa	taccgcaggc	aattgtaaca	1500
cagtgggtgag	tatttgtgtt	tacaaacata	ggaaaggtag	agtaaaacta	tggattataca	1560
atgttatggg	accaccgtca	tgtaagtggt	atgtctttga	cagaaacatg	gttacgtggg	1620
tcatgactgt	atattcactg	gaagatagtc	aagactaaag	acacattaga	gcaaattgac	1680
ccctttaaca	tgtgattatt	gtccaattaa	agacagttga	tttaagtagc	aaaaaaaaaa	1740
aaaaaaa						1747

<210> 94  
 <211> 600  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (553)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (560)  
 <223> n equals a,t,g, or c

<220>  
 <221> SITE  
 <222> (589)  
 <223> n equals a,t,g, or c

<400> 94	
gaattcggca	cgagcggcac
tgctggaact	gagtacttcc
ttactgggtc	ctcaccgtst
tccccagggtg	ccctggacaa
cctctctgcc	gctgtttag
caacagctgg	gcgccctcat
tacatatttc	agttttawag
aattaaaagg	aaaaaaaaag
attcccagag	aattgtattt
attgtgggtt	gtnacaattn
gagccgagat	cgttctgggg
gggtccccgc	atttggctgg
tcttctcat	tatctacata
cagtggcct	gtgctttaac
cgtctccct	gagaaggaca
cgttctttgc	cttctctggc
caggaccata	cagtgtttta
actgtaaaaa	cagctgtagg
tgttttttat	attcttaaat
ctttatttgg	caagtgttnt
ctgctggtat	ggacgcttat
gtcatgtttg	tagctgtatt
acaatgacct	acaccaggat
ggcagtgcc	tcgtcttgta
gtcacaactt	
acgctggaaa	
ccattttgat	
tataatgtat	
ttgctcacia	
aggcttttaa	

<210> 95  
 <211> 586



&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 95

ggcacgaggt	tttttccttt	ataacggaag	ttttataatt	catcttttat	gtaagtgtaa	60
ttctcattaa	aaatacccta	aagcttaaag	tttgcaaggc	tgcccagcct	aaccacaaac	120
agtttgatgc	tgccccctag	cgtttgatgc	ccttcacctt	ttgctaaaat	aaggtaatgt	180
ttaaattaca	attagattta	cttactgctg	taaatctggt	ctatttttagt	ttcctctggg	240
tagttagtgt	tgctaataag	atggacgtaa	gtgtttttga	actgggtgaat	tctgattgct	300
tttagcccc	agttttccaa	ataggggtga	attttggtga	gagatagaac	aatcaccaag	360
ttaccttgct	ccaaaaaaga	aattttacgta	tgggattggt	ttcaaagcgg	gaagttagct	420
gtgtaaataa	caacaatttt	atataattta	tctgggcttc	tccttatctt	gaatgatata	480
aaaatctact	ttctagatta	atttagttcc	atataacttt	gtattgcttt	gactgtactg	540
ataataaagt	ttgaaagtgt	taaaaaaaaa	aaaaaaaaaa	aaaaaa		586

&lt;210&gt; 96

&lt;211&gt; 802

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 96

ggcacgagcc	ctcctccctg	ctcgccecca	gattcccctc	ccctccctgg	tgcttttgtc	60
tggagggtgt	tatgggtttg	tgtgtgtatg	agcgtgtgtg	tgtttttgga	tttcagacta	120
attttctgga	gtttctgccc	ctgctctgcg	tcaccctcac	gtcacttcgc	cagcagtagc	180
agaggcggcg	gcggcggctc	cgggaattgg	gttggagcag	gagcctcgct	ggctgcttcg	240
ctcgcgctct	acgcgctcag	tccccggcgg	tagcaggagc	ctggaccag	gcgcgcggg	300
cgggcgtgag	gcgcgggagc	cggggtgagc	agcgcagata	gtgccctcgg	tcgcctcggc	360
cctcactgtc	tccccctggg	gcggcctcgg	ctactcccca	ggtgggacgt	gccgcgccac	420
ctgcccgcg	caccggcacc	cagcggcctg	ggcggattct	gcagcatcat	tcggggggccc	480
cgtcgcggag	ccaaagccgc	cggcagtcct	cgcattcccc	tttaaagggt	ccttcgccccg	540
gcctgtacca	tggaatcctg	tcttggggac	cctttcccta	cctccctccc	cctggcctca	600
ggctcgaaga	gagagtgggc	acactggtgg	ctccagcggc	gtcagtgcc	tcgcgggggca	660
agttgattcc	tgggcactca	tccatccaca	gtctccgggc	tggggtcggg	gtggggatga	720
cgcgagcaga	gagggagagt	gcccccaatta	gtggtgttgg	gggtcctacg	ctcagttctta	780
cgcgtgtctg	tttgtcctca	gc				802

&lt;210&gt; 97

&lt;211&gt; 1226

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 97

ggcacgagca	tgctttgctt	acaatggagt	ctgcagtgag	gggagatgct	gggatagcca	60
tttccatggc	tctgttatgc	aagcacaaat	ttcatctcct	agatggactt	cctgggttttc	120
tcttactgca	gtaacactgg	ccttcccttc	tctaattcct	taccccagct	gcggcatccc	180
tgtgttaact	caggatgcc	agtggccctc	agattacact	tctccagata	gctgaatgag	240
tctgctttca	ctgtgactgg	gacctgaatg	acctgcagtc	agggcccaga	gttgggactc	300
tatactaccc	tgggctctgg	tctgtagggt	tgtagtagcc	accggttaata	agccaagggc	360
taggctcttg	tttgagttaa	tggccacctg	gaattttcag	tcatctcatg	atacaggcgg	420
gaggggcaga	acagatagat	tacgacaggt	ttgggtttta	aattttccaa	ccaagtggaa	480
aggcaagtgt	gtcttataga	aagcactact	gcacttagta	gctatgtgat	tttgagcaaa	540
ccacataatc	tctctaggtc	cattttccta	accacaagat	aaagatgtta	cattgtcaaa	600
gcttgccgta	gatttggggg	gaatgaaaat	tattccttgc	tttcatcact	acctttatag	660

ctctcatcac	tacctttata	gctcatcact	gtgccttttt	ttctttccta	agaaagacat	720
cacatccctc	tectctectc	ctctgtgctc	ctgtccctcc	ctccccctag	caaggtccag	780
gcaaagctgg	agatgaagct	gaagatccag	agtttcctag	aacgcaactt	aaggatggct	840
aaggaaaggg	aagcctgact	gctcggtcag	gaggggtgcag	tatctcttgc	tgggaacaca	900
gccagtttcc	acaatgccta	gactgtgtat	gtctatttgc	acaagattgg	cttttcctat	960
tttggagtgg	tcagacattt	tatttttgtt	caagattatc	tggcggttta	gacaaatttg	1020
caaaactgtg	cttttattga	ctttttgaat	aaactttggt	attctggagc	aaatgtattt	1080
atattattgg	atgtgcaatg	acaaacttgg	tatttttccc	atgtttgaca	tttatgttat	1140
gtttgttaga	attttagtgt	ttgtctaagt	acacacatat	atcaacaaat	taaacttgaa	1200
tcgtttcaaa	aaaaaaaaaa	aaaaaa				1226

&lt;210&gt; 98

&lt;211&gt; 1120

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 98

aggggactct	caccctctcc	cagcaatgtc	taaagtcagg	catctgaaaa	ccagcagtaa	60
tectgectct	gaagtttata	aggaaaggag	cttaaaagag	aaccaaattc	agcctgtgtt	120
ggaactctca	gtcccagagg	ggtgtggttt	atagctctcc	ggcctgctgt	tggacttagg	180
ctgtgaccca	cagaaggacg	ccagaaagta	ctcaagacat	tcacggtgcc	ccggtcagca	240
ctcgccatga	cgaagacttc	tacatgcata	taccacttcc	ttgttctgag	ctggtatact	300
ttcctcaatt	attacatctc	acaggaagga	aaagacgagg	tgaaacccaa	aatcttggca	360
aatggtgcaa	ggtggaaata	tatgacgtg	cttaatctgc	tcttgacagc	cattttctac	420
ggggtcacct	gcctggatga	tgtgctgaaa	agaaccaaag	ggggaaaaga	cattaagttc	480
ctaactgcct	tcagagacct	gcttttcacc	actctggctt	ttcctgtatc	cacgtttgta	540
tttttggcat	tctggatcct	ctttctctac	aatcgagatc	tcatttacct	caaggctcta	600
gatactgtca	tccccgtgtg	gctgaatcat	gcaatgcaca	ctttcatatt	ccccatcaca	660
ttggctgaag	tcgtcctcag	gcctcactcc	tatccatcaa	agaagacagg	actcaccttg	720
stggctgctg	ccagcattgc	ttacatcagc	cgcacccat	ggctctactt	tgagacgggt	780
acctgggtgt	atcctgtgtt	tgccaaactc	agcctcttgg	gtctagcagc	tttcttctct	840
ctcagctacg	tcttcacgcg	cagcatctac	ctacttggag	agaagctcaa	ccactggaaa	900
tggggtgaca	tgaggcagcc	acggaagaag	aggaagtaat	tgcacacccat	tttccaagaa	960
ccaagaaaga	agaaaacaca	agagattttt	ctcatctttt	tttttttttt	tctgggtggag	1020
ggaggtggtg	gaggaacata	gcaaagtagg	agggacagag	agtgatactt	aaatttaata	1080
agaggttcgt	gaaggtaaaa	aaaaaaaaaa	aaaactcgag			1120

&lt;210&gt; 99

&lt;211&gt; 2596

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 99

ccacgcgtcc	gacttggcaa	gcgttcacaa	ccaaaatggc	cagctctttc	tgggaagatat	60
tgtaaaacgt	gatggatttc	cactatgggt	tgggctctca	agtcattgatg	gaagtgaatc	120
aagttttgaa	tgggtctgatg	gtagtacatt	tgactatatc	ccatggaaaag	gccaaacatc	180
tectggaaat	tgtgttctct	tggatccaaa	aggaacttgg	aaacatgaaa	aatgcaactc	240
tgttaaggat	ggtgtctattt	gttataaaac	tacaaaatct	aaaaagctgt	cccgtcttac	300
atattcatca	agatgtccag	cagcaaaaaga	gaatgggtca	cgggtggatcc	agtacaaggg	360
tcactgttac	aagtctgata	aggcattgca	cagtttttca	gaggccaaaa	aattgtgttc	420
aaaacatgat	cactctgcaa	ctatcgtttc	cataaaagat	gaagatgaga	ataaatttgt	480
gagcagactg	atgagggaaa	ataataacat	taccatgaga	gtttggcttg	gattatctca	540
acattctgtt	gaccagtctt	ggagttggtt	agatggatca	gaagtgcacat	ttgtcaaatg	600

ggaaaaataaaa	agtaagagtg	gtgttggaag	atgtagcatg	ttgatagctt	caaatgaaac	660
ttggaaaaaaa	gttgaatgtg	aacatgggtt	tggaagagtt	gtctgcaaag	tgcctctggg	720
ccctgattac	acagcaatag	ctatcatagt	tgccacacta	agtatcttag	ttctcatggg	780
cggactgatt	tggttcctct	tccaaaggca	ccgtttgcac	ctggcggtt	tctcatcagt	840
tcgatatgca	caaggagtga	atgaagatga	gattatgctt	ccttctttcc	atgactaaat	900
tcttctaaaa	gttttcta	ttgcactaat	gtgttatgag	aaattagtca	cttaaaatgt	960
cccagtgtca	gtatttactc	tgtcccaaag	tagaactctt	aaatactttt	tcagttgttt	1020
agatcttagg	catgtgctgg	tatccacagt	taattccctg	ctaaatgcca	tgtttatcac	1080
cctaattaat	agaatggagg	ggactccaaa	gctggaactg	aagtccaaat	tgtttgtaca	1140
gtaatatgtt	taatgttcat	tttctctgta	tgaatgtgat	tggttaactag	atatgtatat	1200
tttaatagaa	tttttaacaa	aacttcttag	aaaattaaaa	taggcatatt	actaggtgac	1260
atgtctactt	tttaattttt	aagagcatcc	ggccaaatgc	aaaattagta	cctcaaagta	1320
aaaattgaac	tgtaaactct	atcagcattg	tttcaaaata	gtcattttta	gcactgggga	1380
aaaataaaca	ataagacatg	cttacttttt	aattttttatt	tttttgagac	tgagtctctc	1440
tctgttgccc	aggctggagt	acaatggcgt	gatctcggct	cactgcaa	ctccgcctcc	1500
caggttcaag	cgattctcct	gcctcagcct	cctgagtagc	tgggattaca	ggcaactgcc	1560
accatgcccg	gctaattttt	gtattttttag	tagagatggg	gtttcaccat	gttggccagg	1620
ctggtctcga	actcgtgacc	gcaggtgatc	ctcccgcctc	ggcctcccaa	agtgtctggga	1680
ttacaggcat	gagccaccgc	gcctggcctc	tgttactttt	ttatatagca	aaatgattcc	1740
tcttggaag	atgtttctta	tattattcca	aagttatttc	ataccattat	tatgtaaata	1800
tgaagagttt	ttttctgttt	ataattgttt	ataaaacaat	gacttttaaa	gatttagtgc	1860
ttaacatttt	cccaagtgtg	ggaacattat	ttttagattg	agtaggtacc	ttgtagcagt	1920
gtgctttgca	ttttctgatg	tattacatga	ctgtttcttt	tgtaaagaga	atcaactagg	1980
tatttaagac	tgataatttt	acaattttata	tgtttcacat	agcatgtcaa	cttttgacta	2040
agaattttgt	ttactttttt	aacatgtgtt	aaacagagaa	aggggtccatg	aaggaaagtg	2100
tatgagttgc	atttgaaaaa	tgagactttt	tcagtggaa	tctaaacctt	gtgatgacta	2160
ctaacaaatg	taaaattatg	agtgattaag	aaaacattgc	tttgtgggta	tcactttaag	2220
ttttgacacc	tagattatag	tcttagtaat	agcatccact	ggaaaagggtg	aaaatgtttt	2280
attcagcatt	taacttacat	ttgtacttta	gagtattttt	gtataaaatc	catagattta	2340
ttttacattt	agagtattta	cactatgata	aagttgtaaa	taatttttcta	agacagtttt	2400
tatatagtct	acagttgtcc	tgattttctta	ttgaatttgt	tagactagtt	ctcttgtctt	2460
gtgatctgtg	tacaatttta	gtcactaaga	ctttcctcca	agaactaagc	caacttgatg	2520
tgaaaagcac	agctgtatat	aatgggtgatg	tcataataaa	gttgttttat	cttttaagta	2580
aaaaaaaaaa	aaaaaa					2596

&lt;210&gt; 100

&lt;211&gt; 1020

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 100

aaactagggg	aaaatgtagc	caacatatac	aaagatcttc	agaaactctc	tcgcctcttt	60
aaagaccagc	tggtgtatcc	tcttctggct	tttaccgcac	aagcactgaa	cctaccagat	120
gtatttggtt	tggtcgtcct	cccattggaa	ctgaaactac	ggatcttccg	acttctggat	180
gttcgttccg	tcttgtcttt	gtctgcggtt	tgtcgtgacc	tctttactgc	ttcaaagac	240
ccactcctgt	ggaggttttt	atatctgcgt	gattttcgag	acaatactgt	cagagttcaa	300
gacacagatt	ggaagactgt	acaggaagag	gcacatacaa	agaaaagaat	ccccgaaagg	360
gcggtttgtg	atgctcctgc	catcgtcaac	tcacaccatt	ccattctatc	ccaaccctt	420
gcaccctagg	ccatttccta	gctcccgcct	tcctccagga	attatcgggg	gtgaatatga	480
ccaaagacca	acacttcctt	atggttgaga	cccaatcagt	tcactcatte	ctggctcctg	540
ggagacgccc	agccagtttc	ctccactgag	accacgcttt	gatccagttg	gcccacttcc	600
aggacctaac	cccattcttg	cagggcgagg	cggccccaat	gacagatttc	ccttttagacc	660
cagcaggggt	cggccaactg	atggccggct	gtcattcatg	tgattgattt	gtaatttcat	720
ttctggagct	ccatttggtt	ttgtttctaa	actacagatg	tcaactcctt	ggggtgctga	780

tctcgagtgt	tattttctga	ttgtggtggt	gagagttgca	ctcccagaaa	cctttttaaga	840
gatacattta	tagccctagg	ggtggtatga	cccaaagggt	cctctgtgac	aagggtggcc	900
ttgggaatag	ttggctgcca	atctccctgc	tcttggttct	cctctagatt	gaagtttgtt	960
ttctgatgct	gttcttacca	gattaaaaaa	aagtgtaaat	taaaaaaaaa	aaaaaaaaaa	1020

&lt;210&gt; 101

&lt;211&gt; 1520

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (71)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (473)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 101

gcttttttct	taagtgcaca	aagcatcata	ctccctggag	gcaaacacat	cgggctgctt	60
cagcgttacg	ngatgcttag	cattttgaat	attgtggcaa	aaaaattaaa	agttcactta	120
ttaatatatta	tcagcagtat	cataatttcc	atcctcttat	ttcagaattt	cacttgaggc	180
aaaaataacca	caagtgtaat	tactctagca	cagctattaa	tgtgctggat	gataggccac	240
tgcgtcacat	gaccttctat	tgttcatggg	tttaaagaga	aagcagggct	ttgtatttct	300
ttttcttctt	ttaaagtcca	ctgtagcatc	ttggcttttg	tctggggtgg	ggaggatctg	360
gggtctgggt	cactttgtaa	aagtaaacca	tgtctgttta	aacaatagag	gtgtttaaga	420
agactcttta	gttttcctgc	agattgttca	agattacatg	ataatcacac	gnggtattta	480
tttctactg	acaaaccaag	tacttgttac	atcaccaatg	gtaccaggag	atgaagacgc	540
gggttttgag	caggagcgag	attaccaccc	aaaaagggag	ctacctgagg	cagcccagct	600
tctagcaaac	tttttacatg	ttgcacattt	cagttcttaa	atgaaggcta	ctccagtgtc	660
atttcattaa	agtacctggg	tgtagtactc	aagtcctccc	tcaagagttc	ataagtaagc	720
agtatccttt	tggccagtgg	tcctgttttt	gccccctacc	agactgttcg	rgaagcatat	780
tctatagata	aatctgacat	ttgtcatcca	ataccattgc	agtcctctgc	agcatacatt	840
ctcaatgggg	gctgtatcac	ccctagattg	gttctgagat	actgcaatgt	cttgtgtcct	900
tccaaaggac	cataatactt	gagcaaatat	gaacatttct	tggggtgagg	gcagaaagag	960
agaaacaaaa	gtctaataag	ggacaataat	gaaaaaacag	ttgagacctt	tagtatgatg	1020
ggaacaggat	gaggaaggag	gagatactga	caggagccct	gggtcttgct	ctgcattaaa	1080
cagatattta	tggacattaa	acagatatatt	atggagcacg	actctgtacc	ctacaggccc	1140
agaatagtct	taaggctcct	gggaattgat	gataggccat	ttaccaggtt	tcagtttaga	1200
ggcagattca	ctggccttag	catttccagta	attatatatta	tttattttta	gcctgaacca	1260
gatttaatat	gagaaactac	tttctgcgtt	tcttttaatt	acttgtagtt	tacacagtaa	1320
ctttagaaga	gtaaatgaaa	gcatgcttcg	atgctgccac	tgtaaatacc	attcattagt	1380
aacttatttt	ccctggagtc	ttgtgaagtg	tgaatttaaa	gcctgctcta	tctggaatat	1440
ggaatagtat	taagattaca	agcacatttt	atattcatga	gccggaaagg	caaaaaaaaaa	1500
aaaaaaaaat	gacctctgag					1520

&lt;210&gt; 102

&lt;211&gt; 1306

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1300)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 102

aattccccggg	tcgacccacg	cgtccggaat	ttaagggacc	cacactacct	tcccgaagtt	60
gaaggcaagc	ggtgattgtt	tgtagacggc	gctttgtcat	gggacctgtg	cgggttgggaa	120
tattgctttt	cctttttttg	gccgtgcacg	aggcttgggc	tgggatgttg	aaggaggagg	180
acgatgacac	agaacgcttg	cccagcaa	gcgaagtgtg	taagctgctg	agcacagagc	240
tacaggcgga	actgagtcgc	accggtcgat	ctcgagaggt	gctggagctg	gggcaggtgc	300
tggatacagg	caagaggaag	agacacgtgc	cttacagcgt	ttcagagaca	aggctggaag	360
aggccttaga	gaatttatgt	gagcggatcc	tggactatag	tggtcacgct	gagcgcaagg	420
gctcactgag	atatgccaa	ggtcagagtc	agaccatggc	aacactgaaa	ggcctagtgc	480
agaagggggg	gaaggtggat	ctggggatcc	ctctggagct	ttgggatgag	cccagcgtgg	540
aggtcacata	cctcaagaag	cagtgtgaga	ccatgttgga	rgargaggag	gaagaggagg	600
aagaggaagg	gggagacaag	atgaccaaga	caggaagcca	ccccaaactt	gaccgagaag	660
atctttgacc	cttgcccttg	agccccagg	aggggaagg	atcatggaga	gccctctaaa	720
gcctgcactc	tcctgtctcc	acagctttca	gggtgtgttt	atgagtgact	ccaccaagc	780
ttgtagctgt	tctctcccat	ctaacctcag	gcaagatcct	ggtgaaacag	catgacatgg	840
cttctggggg	ggaggggtgg	gggtggaggtc	ctgctcctag	agatgaactc	tatccagccc	900
cttaattggc	aggtgtatgt	gctgacagta	ctgaaagctt	tcctctttaa	ctgatcccac	960
ccccacccaa	aagtcagcag	tggcactgga	gctgtgggct	ttggggaagt	cacttagctc	1020
cttaagggtct	gttttttagac	ccttccaagg	aagaggccag	aacggacatt	ctctgcgac	1080
tatatacatt	gcctgtatcc	aggaggctac	acaccagcaa	accgtgaagg	agaatgggac	1140
actgggtcat	ggcctggagt	tgctgataat	ttaggtggga	tagatacttg	gtctacttaa	1200
gctcaatgta	accagagcc	caccatatag	ttttataggt	gctcaatttt	ctatatcgct	1260
attaaacttt	tttctttttt	tctaaaaaaa	aaaaaaaaan	actcga		1306

&lt;210&gt; 103

&lt;211&gt; 785

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 103

cttttagaag	gtacgcctgc	aggtaccggt	ccggaattcc	cgggtcgacc	cacgcgtccg	60
ggaaatgaac	taccatttat	aacttctgtt	tttttattga	gaaaatgatt	cacgaattcc	120
aaatcagatt	gccaggaaga	aataggacgt	gacggtactg	ggccctgtga	ttctcccagc	180
ccttgcagtc	cgctaggtga	gaggaaaagc	tctttacttc	cgccctggc	agggacttct	240
gggttatggg	agaaaccaga	gatgggaatg	aggaaaatat	gaactacagc	agaagcccct	300
gggcagctgt	gatggagccc	ctgacattac	tcttcttgca	tctgtcctgc	cttctttccc	360
tctgcgaggc	agtgggggtg	gattcagagt	gcttagtctg	ctcactggga	gaagaagagt	420
tcctgcgcct	gcaagcccctg	ctgtgtggct	gtcgttttaca	tttgggaggt	gtcctgtatg	480
tctgtacgtt	ggggactgct	tgtatttgga	agattttaaaa	acctagcacc	ctgtttctcac	540
cctctaagct	gcattgagaa	atgactcgtc	tctgtatttg	tattaagcct	taacactttt	600
cttaagtga	ttcgggtgcca	acatttttta	gagctgtacc	aaaacaaaaa	gcctgtactc	660
acatcacaat	gtcatttttg	taggagcggt	ttgttatttt	tacaaggcag	aatgggggtg	720
aacagttgaa	ttaaacttag	caatcacgtg	ctcaaaaaaa	aaaaaaaaaa	aaaaagggcg	780
gccgc						785

&lt;210&gt; 104

&lt;211&gt; 2015

&lt;212&gt; DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1981)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (1990)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2001)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2002)

<223> n equals a,t,g, or c

<400> 104

ccnggaatnc	cggtcgacc	cacgcgtccg	gcctgcgctg	ccagcagcca	ggagccagga	60
gccaagagca	gagcgccagc	atgaacttgg	gggtcagcat	gctgaggatc	ctcttctctc	120
tggatgtagg	aggagctcaa	gtgctggcaa	caggcaagac	ccctggggct	gaaattgatt	180
tcaagtacgc	cctcatcggg	actgctgtgg	gtgtcgccat	atctgctggc	ttcctggccc	240
tgaagatctg	catgatcagg	aggcacttat	ttgacgacga	ctcttccgac	ctgaaaagca	300
crcttggggg	cctcagtgc	accatcccgc	taaagaagag	agccccaagg	cgaaaccaca	360
atttctccaa	aagagatgca	caggtgattg	agctgtaggt	gagcagtgc	gtgaagaggg	420
gttctagccc	cgtggaaaac	agcccatggt	taacatctca	ggatgtcctg	cattcaaaca	480
cccaaggctg	gtaatgaact	ttcacatgga	ctgaatattg	gaggcaaata	atagaaggaa	540
tagaatatac	agtgcctctg	tcctgaagga	aaatatcatg	cctcttctgg	aagaaacgga	600
ctgcacagag	gaaggattga	gcaatttagc	ctgcagtggg	agaagggtga	caccaaagc	660
ttcacccctgt	gttggagctg	ttcatgcttc	catgaggcca	tgggtgtccat	gtccgtggaa	720
cctaccacag	aaaatggctc	atgaaaaggg	gaatccgacc	caacacacag	cttctctacac	780
actgccatct	tatcaacagt	taggcactac	tttgtagaac	gattagcttc	accctcttag	840
ctgccaggag	atcccttctt	aaagatggac	tatgtgaaga	ttcgggagtc	ctgaaacatg	900
gggactccgg	gatggtctct	agccctatcg	atgatgaaca	ctggccttct	ggaggggaaa	960
tggcagtctg	ggctggcgctg	gtaggaaggg	ctttgggtgt	catggaatgg	gcctgctgct	1020
ctcagacctt	caaaggatgg	aaccaacgaa	ggaccaaatg	agaaagcaga	tgcttgccct	1080
gcagagggcc	atgaatgtca	gttattatct	ttctccttat	acaattatct	tgtggttatt	1140
attacaatgt	acatggctgt	tgcatagaag	acatgactgg	tggaggctga	ggaaagccat	1200
gacattctac	aattgccatc	aggctaaggc	cccgtgagca	tttctctccc	ttgtaatat	1260
aacctgtat	ttctgggatc	acatcacgga	atattctttg	cctttccact	ttccaggaaa	1320

tctctcggac	tgggctaccc	tccttgtgtg	tgatgaaaga	tgagctatat	ttcagaacaa	1380
agtgtgtgt	tgtcatratt	tgcctggact	cccagggcgt	ctcttaccca	acttgataac	1440
gatgtgttc	attagcagcc	tttgtttaact	gataaccaag	agcggtaatg	tgatactcat	1500
aagcaatttt	ctgtgtgtag	gataaaaataa	accatcttgt	atgggaaaaa	aaaaaaaaaa	1560
aaaaaaaaaa	aaaaagggcg	gccgctctag	aggatccaag	cttacgtacg	cgtgcatgcg	1620
acgtcatagc	tcttctatag	tgkacaccta	attcaattca	ctggccgtcg	ttttacaacg	1680
tcgtgactgg	gaaaaccctg	gcgttaccca	acttaatcgc	cttgacgac	atcccccttt	1740
cgccagctgg	cgtaatagcg	aagaggcccc	caccgatcgc	ccttcccaac	agttgcgag	1800
cctgaatggc	gaatgggacg	cgccctgtag	cgggcgatta	agcgcggcgg	gtgtggtggt	1860
tacgcgcagc	gtgaccgcta	cacttgccag	cgccctagcg	cccgtcctt	tcgctttctt	1920
cccttccttt	ctcgccacgt	tcgccgggtt	tccccgtcaa	gctttaaatc	gggggcttcc	1980
nttaagggtg	ccaattaagg	nnttaccggg	acctt			2015

&lt;210&gt; 105

&lt;211&gt; 367

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 105

cggcacgagt	gtaaatgtca	ccaccaaaagg	tttgcaccct	gatcaaaaag	agtatgaaaa	60
gaataatacc	acaacactta	tggcctgtct	tggaggcctt	ctggggatta	ttggtgtgat	120
atgtcttata	agctgcctct	ctccagaaat	gaactgtgat	ggtggacaca	gctatgtgag	180
gaattactta	cagaaaccaa	cctttgcatt	aggtgagctt	tatcctcttc	tgataaatct	240
ctgggaagca	ggaaaagaaa	aaagtacatc	actgaaagta	aaagcaactg	ttataggttt	300
accaacaaat	atgtcctaaa	aaccaccaag	gaaacctact	ccaaaaatga	aaaaaaaaaa	360
aaaaaaa						367

&lt;210&gt; 106

&lt;211&gt; 1889

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 106

ctcatccttc	tatcatcata	tggagtggca	ataatgaaaa	tgaggaggcg	ctgatgatga	60
attggtatca	tatcagtttc	actgaccggc	caatctacat	caaggactat	gtgacactct	120
atgtgaaaaa	catcagagag	ctcgtactgg	caggagacaa	gagtcgtcct	tttattacgt	180
ccagtcctac	aaatggggct	gaaactgttg	cagaagcctg	ggtctctcaa	aaccctaata	240
gcaattattt	tggatgatga	catttttatg	actatatcag	tgattgctgg	aactggaaag	300
ttttcccaaa	agctcgattt	gcattctgaat	atggatatca	gtcctggccg	tccttcagta	360
cattagaaaa	ggtctcgtct	acagaggact	ggtctttcaa	tagcaagttt	tcacttcatc	420
gacaacatca	cgaagggtgg	aacaaacaaa	tgtctttatca	ggctggactt	catttcaaac	480
tccccaaaag	cacagatcca	ttacgcacat	ttaaagatac	catctacctt	actcagggtga	540
tgcaggccca	gtgtgtcaaa	acagaaactg	aattctaccg	ccgtagtcgc	agcgagatag	600
tggatcagca	agggcacacg	atgggggcac	tttattggca	gttgatgac	atctggcaag	660
ctccttcctg	ggcttctctt	gatacggagg	aaagtggaaa	atgcttcatt	actttgctca	720
gaattttctt	gctccactgt	tgccagtagc	tttgaaatga	aaacatgttc	tatatctatg	780
gtgtgtcaga	tcttactcgc	gattattcga	tgacactcag	tgtgagagtc	catacatgga	840
gtcccttgga	gcccggtg	tctcgtgtga	ctgaacgttt	tgtgatgaaa	ggaggagagg	900
ctgtctgcct	ttatgaggag	ccagtgtctg	aattgctgag	gagatgtggg	aattgcacac	960
gggaaagctg	tgtggtttcc	ttttaccttt	cagctgacca	tgaactcctg	agcccgacca	1020
actaccactt	cctgtcctca	ccgaaggagg	ccgtggggct	ctgcaaggcg	cagatcactg	1080
ccatcatctc	tcagcaaggt	gacatatattg	tttttgacct	ggagacctca	gctgtcgtc	1140
cctttgtttg	gttggatgta	ggaagcatcc	caggagagatt	tagtgacaat	ggtttcctca	1200

tgactgagaa	gacacgaact	atattatattt	acccttgagg	gccaccagc	aagaatgagt	1260
tggagcaatc	ttttcatgtg	acctccttaa	cagatattta	ctgaaggaa	ctagggtgta	1320
ttttcagtg	acaatgggaa	taaagcattt	ctaaagcacc	gactggagag	gaaggcaaca	1380
gagacaagga	gagaagccga	gagacatgtc	tgcgtgctgc	cacgcacatc	agcgattgct	1440
ctgtgaagag	ttgtacactg	aacattttca	ggggaggctg	tttaccagc	caatgtcctc	1500
aaacaagcct	gtgccggggt	gtcctggaat	ctgtgccagg	actgtgtttt	tagcccttca	1560
cctctcagct	ttagcaggac	atgaaccagt	tataacaaga	tggccctgca	gctgggttaca	1620
agaatgtgac	atggcaggat	ctatggaacc	aaatggaagg	ttttgagggt	atgtagggtc	1680
ttcacagtta	gctttgggga	atacagaata	ctcaaataaa	gtgctttgtt	attatttcag	1740
aggggaatgg	gattgaaatg	ttacaacaga	gatttcttgg	tggtagctat	ttgggtaaag	1800
gtatatggat	atttttctgt	acatgtgaaa	ttatataaaa	ataaaagtta	tataaattac	1860
attgaaaaaa	aaaaaaaaaa	aaaaaaaaaa				1889

&lt;210&gt; 107

&lt;211&gt; 1201

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1086)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1161)

&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (1176)

&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 107

cggcacgagc	ggctggcagc	acgactcgcg	taccgtgcgc	cgattgcctc	tcggcctggg	60
caatgggtccc	ggctgccggg	cgacgaccgc	cccgcgtcat	gcggctcctc	ggctgggtggc	120
aagtattgct	gtgggtgctg	ggacttcccg	tccgcggcgt	ggagggaacct	tatggatttt	180
ctgaacccaa	acggtagtga	ctgtactcta	gtcctgtttt	acaccccgctg	gtgccgcttt	240
tctgccagtt	tggcccttca	ctttaactct	ctgccccggg	catttccagc	tcttcaactt	300
ttggcactgg	atgcactctca	gcacagcagc	ctttctacca	ggtttggcac	cgtagctggt	360
cctaataattt	tattatttca	aggagctaaa	ccaatggcca	gatttaataca	tacagatcga	420
acactggaaa	cactgaaaat	cttcattttt	aatcagacag	gtatagaagc	caagaagaat	480
gtggtggtaa	ctcaagccga	ccaaataggc	cctcttccca	gcactttgat	aaaaagtgtg	540
gactgggtgc	ttgtattttc	cttattcttt	ttaattagtt	ttattatgta	tgctaccatt	600
cgaactgaga	gtattcgggtg	gctaattcca	ggacaagagc	aggaacatgt	ggagtagtga	660
tgggtctgaaa	gaagtgggaa	agaggaactt	caatccttcg	tttcagaaat	tagtgctaca	720
gtttcataca	ttttctccag	tgacgtgttg	acttgaaaact	tcaggcagat	taaaagaatc	780
atattgtttaa	caactgaatg	tataaaaaaa	ttataaaactg	gtgttttaac	tagtattgca	840
ataagcaaat	gcaaaaatat	tcaatagatg	cactattctt	gtttttactg	catgmactga	900
atccagtatt	tggkaaagta	atccaktttg	aaatgtgrag	rtgtattccg	gcagaatagt	960
gagtagaatg	acagcttact	atacagaagg	cmaaaatagg	actctcaggt	aatagtttaa	1020
ggaaaccctt	gattccttat	gatgatgttt	aagaaagggt	agttttctgt	ttctttgcca	1080
gttttnttc	taggagtcca	tagccaggga	aagtatgtga	accagaattg	gttagtgtga	1140
ccccctccaa	gtagccagtg	ntgggaaata	agggtncaat	accttgatgt	ttgtgatctc	1200



t

1201

<210> 108  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (75)  
 <223> Xaa equals stop translation

<400> 108

Met	Asp	Pro	Leu	Cys	Leu	Pro	Ile	Ile	Leu	Phe	Ser	Ala	Val	Val	Leu
1				5					10					15	
Arg	Asn	Leu	Phe	His	Leu	Leu	Ile	Leu	Thr	Phe	His	Tyr	Leu	Pro	Leu
			20					25					30		
Phe	Cys	Asp	Asn	Pro	Leu	Ile	Leu	Glu	Asp	Leu	Ser	Cys	Ile	His	Leu
	35						40					45			
Arg	Val	Asn	Ile	Phe	Lys	Ala	Lys	Gln	Pro	Lys	Phe	Tyr	Gly	Asn	Gln
	50					55					60				
Leu	Gln	Pro	Cys	Val	Met	Lys	Ser	Ser	Ala	Xaa					
65					70					75					

<210> 109  
 <211> 202  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (202)  
 <223> Xaa equals stop translation

<400> 109

Met	Lys	Leu	Leu	Ile	Leu	Phe	Leu	Ser	His	Leu	Leu	Ser	Leu	Ala	Phe
1				5					10					15	
Gly	Ile	Leu	Cys	Leu	Ser	Val	Thr	Val	Ile	Leu	Ser	Leu	Leu	Leu	Ser
			20					25					30		
Phe	Ser	Lys	Arg	Gly	Phe	Ser	Val	Arg	Ser	Phe	Gly	Thr	Gly	Thr	His
		35					40					45			
Val	Lys	Leu	Pro	Gly	Pro	Ala	Pro	Asp	Lys	Pro	Asn	Val	Tyr	Asp	Phe
	50					55					60				
Lys	Thr	Thr	Tyr	Asp	Gln	Met	Tyr	Asn	Asp	Leu	Leu	Arg	Lys	Asp	Lys
65					70					75					80

Glu Leu Tyr Thr Gln Asn Gly Ile Leu His Met Leu Asp Arg Asn Lys  
                     85                    90                    95  
 Arg Ile Lys Pro Arg Pro Glu Arg Phe Gln Asn Cys Lys Asp Leu Phe  
                     100                    105                    110  
 Asp Leu Ile Leu Thr Cys Glu Glu Arg Val Tyr Asp Gln Val Val Glu  
                     115                    120                    125  
 Asp Leu Asn Ser Arg Glu Gln Glu Thr Cys Gln Pro Val His Val Val  
                     130                    135                    140  
 Asn Val Asp Ile Gln Asp Asn His Glu Glu Ala Thr Leu Gly Ala Phe  
                     145                    150                    155                    160  
 Leu Ile Cys Glu Leu Cys Gln Cys Ile Gln His Thr Glu Asp Met Glu  
                     165                    170                    175  
 Asn Glu Ile Asp Glu Leu Leu Gln Glu Phe Glu Glu Lys Ser Gly Arg  
                     180                    185                    190  
 Thr Phe Leu His Thr Val Cys Phe Tyr Xaa  
                     195                    200

&lt;210&gt; 110

&lt;211&gt; 371

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (31)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (193)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 110

Met Gly Leu Lys Leu Leu Gln Lys Pro Gly Ser Leu Lys Thr Leu Ile  
           1                    5                    10                    15

Ala Ile Ile Leu Val Met Tyr Ile Phe Met Thr Ile Ser Val Xaa Cys  
                     20                    25                    30

Trp Asn Trp Lys Val Phe Pro Lys Ala Arg Phe Ala Ser Glu Tyr Gly  
                     35                    40                    45

Tyr Gln Ser Trp Pro Ser Phe Ser Thr Leu Glu Lys Val Ser Ser Thr  
                     50                    55                    60

Glu Asp Trp Ser Phe Asn Ser Lys Phe Ser Leu His Arg Gln His His

65		70		75		80
Glu Gly Gly Asn Lys Gln Met Leu Tyr Gln Ala Gly Leu His Phe Lys	85	90		95		
Leu Pro Gln Ser Thr Asp Pro Leu Arg Thr Phe Lys Asp Thr Ile Tyr	100	105		110		
Leu Thr Gln Val Met Gln Ala Gln Cys Val Lys Thr Glu Thr Glu Phe	115	120		125		
Tyr Arg Arg Ser Arg Ser Glu Ile Val Asp Gln Gln Gly His Thr Met	130	135		140		
Gly Ala Leu Tyr Trp Gln Leu Asn Asp Ile Trp Gln Ala Pro Ser Trp	145	150		155		160
Ala Ser Leu Glu Tyr Gly Gly Lys Trp Lys Met Leu His Tyr Phe Ala	165	170		175		
Gln Asn Phe Phe Ala Pro Leu Leu Pro Val Gly Phe Glu Asn Glu Asn	180	185		190		
Xaa Phe Tyr Ile Tyr Gly Val Ser Asp Leu His Ser Asp Tyr Ser Met	195	200		205		
Thr Leu Ser Val Arg Val His Thr Trp Ser Ser Leu Glu Pro Val Cys	210	215		220		
Ser Arg Val Thr Glu Arg Phe Val Met Lys Gly Gly Glu Ala Val Cys	225	230		235		240
Leu Tyr Glu Glu Pro Val Ser Glu Leu Leu Arg Arg Cys Gly Asn Cys	245	250		255		
Thr Arg Glu Ser Cys Val Val Ser Phe Tyr Leu Ser Ala Asp His Glu	260	265		270		
Leu Leu Ser Pro Thr Asn Tyr His Phe Leu Ser Ser Pro Lys Glu Ala	275	280		285		
Val Gly Leu Cys Lys Ala Gln Ile Thr Ala Ile Ile Ser Gln Gln Gly	290	295		300		
Asp Ile Phe Val Phe Asp Leu Glu Thr Ser Ala Val Ala Pro Phe Val	305	310		315		320
Trp Leu Asp Val Gly Ser Ile Pro Gly Arg Phe Ser Asp Asn Gly Phe	325	330		335		
Leu Met Thr Glu Lys Thr Arg Thr Ile Leu Phe Tyr Pro Trp Glu Pro	340	345		350		
Thr Ser Lys Asn Glu Leu Glu Gln Ser Phe His Val Thr Ser Leu Thr	355	360		365		

Asp Ile Tyr  
370

<210> 111  
<211> 114  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (38)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (114)  
<223> Xaa equals stop translation

<400> 111  
Met Arg Pro Leu Leu Leu Gly Gly Tyr Trp Val Leu Cys Leu Ser Val  
1 5 10 15

Leu Gly His Ala Ala Leu Tyr His Phe Trp Leu Arg Glu Glu Gly Lys  
20 25 30

Gly Pro Pro Gln Val Xaa Ser Val Leu Ala Leu Ala Leu Pro Ala Gly  
35 40 45

Ser Cys Ala Pro Gly Leu Pro Phe Pro Gly Pro Leu Ile Pro Thr Gln  
50 55 60

Leu Leu Phe Ala Leu Glu Trp Gly Thr Pro Thr Pro Leu Arg Asp His  
65 70 75 80

Pro Pro His Ser Met His Ser Ala Pro Gln Asn Pro Pro Val Phe Leu  
85 90 95

Gly Thr His Thr Cys Pro Pro Ser Trp Tyr Phe Arg Leu Ile Pro Gln  
100 105 110

Ala Xaa

<210> 112  
<211> 152  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (152)  
<223> Xaa equals stop translation

&lt;400&gt; 112

Met Arg Arg Leu Leu Leu Val Thr Ser Leu Val Val Val Leu Leu Trp  
 1 5 10 15

Glu Ala Gly Ala Val Pro Ala Pro Lys Val Pro Ile Lys Met Gln Val  
 20 25 30

Lys His Trp Pro Ser Glu Gln Asp Pro Glu Lys Ala Trp Gly Ala Arg  
 35 40 45

Val Val Glu Pro Pro Glu Lys Asp Asp Gln Leu Val Val Leu Phe Pro  
 50 55 60

Val Gln Lys Pro Lys Leu Leu Thr Thr Glu Glu Lys Pro Arg Gly Gln  
 65 70 75 80

Gly Arg Gly Pro Ile Leu Pro Gly Thr Lys Ala Trp Met Glu Thr Glu  
 85 90 95

Asp Thr Leu Gly Arg Val Leu Ser Pro Glu Pro Asp His Asp Ser Leu  
 100 105 110

Tyr His Pro Pro Pro Glu Glu Asp Gln Gly Glu Glu Arg Pro Arg Leu  
 115 120 125

Trp Val Met Pro Asn His Gln Val Leu Leu Gly Pro Glu Glu Asp Gln  
 130 135 140

Asp His Ile Tyr His Pro Gln Xaa  
 145 150

&lt;210&gt; 113

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 113

Met Pro Cys Gly Lys Phe Leu Phe Pro Val Ser Pro Val Ser Ser Leu  
 1 5 10 15

Ser Leu His Trp Ser Ala Val Leu Leu Leu Leu Ala Asp Phe Pro  
 20 25 30

Arg Val His Gly Ser Pro Pro Gly Val Ser Arg Val Ser Ile Leu His  
 35 40 45

Cys Leu Phe Pro Phe Leu Ser Xaa  
 50 55

<210> 114  
 <211> 237  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (237)  
 <223> Xaa equals stop translation

<400> 114  
 Met Glu Val Arg Leu Ile Phe Leu Ser Gly Leu Cys Ile Ala Val Ala  
     1                    5                    10                    15  
 Val Val Trp Ala Val Phe Arg Asn Glu Asp Arg Trp Ala Trp Ile Leu  
                     20                    25                    30  
 Gln Asp Ile Leu Gly Ile Ala Phe Cys Leu Asn Leu Ile Lys Thr Leu  
                     35                    40                    45  
 Lys Leu Pro Asn Phe Lys Ser Cys Val Ile Leu Leu Gly Leu Leu Leu  
                     50                    55                    60  
 Leu Tyr Asp Val Phe Phe Val Phe Ile Thr Pro Phe Ile Thr Lys Asn  
                     65                    70                    75                    80  
 Gly Glu Ser Ile Met Val Glu Leu Ala Ala Gly Pro Phe Gly Asn Asn  
                     85                    90                    95  
 Glu Lys Leu Pro Val Val Ile Arg Val Pro Lys Leu Ile Tyr Phe Ser  
                     100                    105                    110  
 Val Met Ser Val Cys Leu Met Pro Val Ser Ile Leu Gly Phe Gly Asp  
                     115                    120                    125  
 Ile Ile Val Pro Gly Leu Leu Ile Ala Tyr Cys Arg Arg Phe Asp Val  
                     130                    135                    140  
 Gln Thr Gly Ser Ser Tyr Ile Tyr Tyr Val Ser Ser Thr Val Ala Tyr  
                     145                    150                    155                    160  
 Ala Ile Gly Met Ile Leu Thr Phe Val Val Leu Val Leu Met Lys Lys  
                     165                    170                    175  
 Gly Gln Pro Ala Leu Leu Tyr Leu Val Pro Cys Thr Leu Ile Thr Ala  
                     180                    185                    190  
 Ser Val Val Ala Trp Arg Arg Lys Glu Met Lys Lys Phe Trp Lys Gly  
                     195                    200                    205  
 Asn Ser Tyr Gln Met Met Asp His Leu Asp Cys Ala Thr Asn Glu Glu  
                     210                    215                    220

Asn Pro Val Ile Ser Gly Glu Gln Ile Val Gln Gln Xaa  
225                      230                      235

<210> 115  
<211> 44  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (44)  
<223> Xaa equals stop translation

<400> 115  
Met Phe Cys Phe Tyr Leu His Phe Ile Phe His Val Leu Ser Tyr Lys  
1                      5                      10                      15  
Leu Asn Pro Leu Leu Phe Phe Ser Cys Ser Cys Phe Cys Phe Ile Leu  
                    20                      25                      30  
Val Phe Leu Phe Pro Asp Tyr His Leu Gly Met Xaa  
                    35                      40

<210> 116  
<211> 65  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (65)  
<223> Xaa equals stop translation

<400> 116  
Met Val Arg His Ile Arg Glu Arg Arg Arg Gln Pro Leu Ala Phe Gln  
1                      5                      10                      15  
Arg Val Leu Leu Ser Leu Cys Leu Leu Glu Gly Ile Trp His Ser Pro  
                    20                      25                      30  
Ala Ala Ala Ala Gly Gly Gly Ser His Cys Ser Ser Trp Pro Ser Leu  
                    35                      40                      45  
Tyr Thr Thr Phe Gln Arg Val Ser Leu Leu Glu Leu Asp Leu Gly Leu  
                    50                      55                      60  
Xaa  
65

<210> 117  
<211> 118  
<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (118)

<223> Xaa equals stop translation

<400> 117

Met Ala Arg Ser Ala Leu Arg Leu Glu Ile Leu Gly Gln Leu Leu Val  
1 5 10 15

Gly Val Ser Ser Cys Cys Ala Glu Ile Arg Ser Arg Ser Tyr Leu Gly  
20 25 30

Phe Cys Trp Lys Asn Ile Gln Asp Glu Arg Lys Lys Lys Ile Ile Leu  
35 40 45

Arg Gly Ser Arg Asn Leu Leu Cys Pro Arg Leu Leu Arg Pro Leu Glu  
50 55 60

Pro Val Gln Ala Lys Gly Thr Gln Ser Val Asp Pro Arg Glu Val Val  
65 70 75 80

Arg Glu Thr Arg Ser Met Ser Thr Leu Pro Ala Asp Phe Cys Leu Leu  
85 90 95

Pro Gln Ala Ser Arg Met Ala Gln Lys Gly Ser Pro Ser Arg Ser Ser  
100 105 110

Leu Gln Leu Leu Phe Xaa  
115

<210> 118

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (65)

<223> Xaa equals stop translation

<400> 118

Met Thr Val Ser Leu Phe Leu Leu Leu Ala Thr Ser Gln Ser Gln Asp  
1 5 10 15

Gly Cys Cys Asp Ser Gly Ser Cys Pro Asn Ser Arg Gln Gln Glu Gly  
20 25 30

His Gly Ala Ala Pro Ala Ser Arg Cys Pro Cys Arg Pro Ser Leu Gln  
35 40 45

Ala Gln Glu Pro Lys Glu Glu Ser Thr Gln Met Trp Cys Ser His Leu  
50 55 60



Xaa  
65

<210> 119  
<211> 43  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (43)  
<223> Xaa equals stop translation

<400> 119  
Met Leu Lys Trp Thr Gly Phe Leu Val Val Leu Val Ala Phe Lys Lys  
1 5 10 15  
Ile Ser Ala Ser Phe Gln Val Asn Tyr Asn Leu Lys Phe Glu Ile Ser  
20 25 30  
Phe Gly Glu Pro Trp Lys Phe Thr Gln Trp Xaa  
35 40

<210> 120  
<211> 48  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (48)  
<223> Xaa equals stop translation

<400> 120  
Met Ser Phe Gly Ile Ser Ile His Thr Cys Thr Tyr Leu Ile Phe Ile  
1 5 10 15  
Ala Phe His Phe Ile Ala Leu Cys Lys Val Thr Phe Phe Thr Asp Ser  
20 25 30  
Arg Phe Gly Asn Pro Met Ser Ile Ser Leu Ser Ala Pro Phe Phe Xaa  
35 40 45

<210> 121  
<211> 140  
<212> PRT  
<213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (140)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 121

Met	Ala	Leu	Gly	Ile	Gln	Lys	Arg	Phe	Ser	Pro	Glu	Val	Leu	Gly	Leu
1				5					10					15	

Cys	Ala	Ser	Thr	Ala	Leu	Val	Trp	Val	Val	Met	Glu	Val	Leu	Ala	Leu
			20					25					30		

Leu	Leu	Gly	Leu	Tyr	Leu	Ala	Thr	Val	Arg	Ser	Asp	Leu	Ser	Thr	Phe
		35						40					45		

His	Leu	Leu	Ala	Tyr	Ser	Gly	Tyr	Lys	Tyr	Val	Gly	Met	Ile	Leu	Ser
	50					55					60				

Val	Leu	Thr	Gly	Leu	Leu	Phe	Gly	Ser	Asp	Gly	Tyr	Tyr	Val	Ala	Leu
65					70					75					80

Ala	Trp	Thr	Ser	Ser	Ala	Leu	Met	Tyr	Phe	Ile	Val	Arg	Ser	Leu	Arg
				85					90					95	

Thr	Ala	Ala	Leu	Gly	Pro	Asp	Ser	Met	Gly	Gly	Pro	Val	Pro	Arg	Gln
			100					105					110		

Arg	Leu	Gln	Leu	Tyr	Leu	Thr	Leu	Gly	Ala	Ala	Ala	Phe	Gln	Pro	Leu
		115					120					125			

Ile	Ile	Tyr	Trp	Leu	Thr	Phe	His	Leu	Val	Arg	Xaa
	130					135					140

&lt;210&gt; 122

&lt;211&gt; 92

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (89)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (92)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 122

Met	Met	Asp	Phe	Leu	Arg	Cys	Val	Thr	Ala	Ala	Leu	Ile	Tyr	Phe	Ala
1				5					10					15	

Ile	Ser	Ile	Thr	Ala	Ile	Ala	Lys	Tyr	Ser	Asp	Gly	Ala	Ser	Lys	Ala
			20					25					30		

Ala Gly Gly Ser Val Pro Asp Thr Arg Ala Val Cys Pro Ser Arg Ser  
35 40 45

Glu Met Gly Arg Glu Leu Gly Ala Ala Ala Ser Arg Glu Gln Gly Val  
50 55 60

Ser Pro Val Met His Pro Ile His Pro Val His Arg Cys Leu Ala Ser  
65 70 75 80

Leu Leu Pro Ser Cys Leu Gln Leu Xaa Ser Thr Xaa  
85 90

<210> 123

<211> 347

<212> PRT

<213> Homo sapiens

**<220>**

<221> SITE

**<222> (242)**

<223> Xaa equals any of the naturally occurring L-amino acids

**<220>**

<221> SITE

$\langle 222 \rangle$  (246)

<223> Xaa equals any of the naturally occurring L-amino acids

**<220>**

<221> SITE

**<222> (347)**

<223> Xaa equals stop translation

<400> 123

Met Arg Arg Gly Ala Gly Ala Ala Arg Gly Arg Ala Ser Trp Cys Trp  
1 5 10 15

Ala Leu Ala Leu Leu Trp Leu Ala Val Val Pro Gly Trp Ser Arg Val  
20 25 30

Ser Gly Ile Pro Ser Arg Arg His Trp Pro Val Pro Tyr Lys Arg Phe  
35 40 45

Asp Phe Arg Pro Lys Pro Asp Pro Tyr Cys Gln Ala Lys Tyr Thr Phe  
50 55 60

Cys Pro Thr Gly Ser Pro Ile Pro Val Met Glu Gly Asp Asp Asp Ile  
65 70 75 80

Glu Val Phe Arg Leu Gln Ala Pro Val Trp Glu Phe Lys Tyr Gly Asp  
85 90 95

Leu Leu Gly His Leu Lys Ile Met His Asp Ala Ile Gly Phe Arg Ser  
100 105 110

Thr Leu Thr Gly Lys Asn Tyr Thr Met Glu Trp Tyr Glu Leu Phe Gln  
 115 120 125  
 Leu Gly Asn Cys Thr Phe Pro His Leu Arg Pro Glu Met Asp Ala Pro  
 130 135 140  
 Phe Trp Cys Asn Gln Gly Ala Ala Cys Phe Phe Glu Gly Ile Asp Asp  
 145 150 155 160  
 Val His Trp Lys Glu Asn Gly Thr Leu Val Gln Val Ala Thr Ile Ser  
 165 170 175  
 Gly Asn Met Phe Asn Gln Met Ala Lys Trp Val Lys Gln Asp Asn Glu  
 180 185 190  
 Thr Gly Ile Tyr Tyr Glu Thr Trp Asn Val Lys Ala Ser Pro Glu Lys  
 195 200 205  
 Gly Ala Glu Thr Trp Phe Asp Ser Tyr Asp Cys Ser Lys Phe Val Leu  
 210 215 220  
 Arg Thr Phe Asn Lys Leu Ala Glu Phe Gly Ala Glu Phe Lys Asn Ile  
 225 230 235 240  
 Glu Xaa Asn Tyr Thr Xaa Ile Phe Leu Tyr Ser Gly Glu Pro Thr Tyr  
 245 250 255  
 Leu Gly Asn Glu Thr Ser Val Phe Gly Pro Thr Gly Asn Lys Thr Leu  
 260 265 270  
 Gly Leu Ala Ile Lys Arg Phe Tyr Tyr Pro Phe Lys Pro His Leu Pro  
 275 280 285  
 Thr Lys Glu Phe Leu Leu Ser Leu Leu Gln Ile Phe Asp Ala Val Ile  
 290 295 300  
 Val His Lys Gln Phe Tyr Leu Phe Tyr Asn Phe Glu Tyr Trp Phe Leu  
 305 310 315 320  
 Pro Met Lys Phe Pro Phe Ile Lys Ile Thr Tyr Glu Glu Ile Pro Leu  
 325 330 335  
 Pro Ile Arg Asn Lys Thr Leu Ser Gly Leu Xaa  
 340 345

&lt;210&gt; 124

&lt;211&gt; 234

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (173)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (234)

<223> Xaa equals stop translation

<400> 124

Met His Arg Gly Lys Leu Asp Cys Ala Gly Gly Ala Leu Leu Ser Ser  
1 5 10 15

Tyr Leu Ile Val Leu Met Ile Leu Leu Ala Val Val Ile Cys Thr Val  
20 25 30

Ser Ala Ile Met Cys Val Ser Met Arg Gly Thr Ile Cys Asn Pro Gly  
35 40 45

Pro Arg Lys Ser Met Ser Lys Leu Leu Tyr Ile Arg Leu Ala Leu Phe  
50 55 60

Phe Pro Glu Met Val Trp Ala Ser Leu Gly Ala Ala Trp Val Ala Asp  
65 70 75 80

Gly Val Gln Cys Asp Arg Thr Val Val Asn Gly Ile Ile Ala Thr Val  
85 90 95

Val Val Ser Trp Ile Ile Ile Ala Ala Thr Val Val Ser Ile Ile Ile  
100 105 110

Val Phe Asp Pro Leu Gly Gly Lys Met Ala Pro Tyr Ser Ser Ala Gly  
115 120 125

Pro Ser His Leu Asp Ser His Asp Ser Ser Gln Leu Leu Asn Gly Leu  
130 135 140

Lys Thr Ala Ala Thr Ser Val Trp Glu Thr Arg Ile Lys Leu Leu Cys  
145 150 155 160

Cys Cys Ile Gly Lys Asp Asp His Thr Arg Val Ala Xaa Ser Ser Thr  
165 170 175

Ala Glu Leu Phe Ser Thr Tyr Phe Ser Asp Thr Asp Leu Val Pro Ser  
180 185 190

Asp Ile Ala Ala Gly Leu Ala Leu Leu His Gln Gln Gln Asp Asn Ile  
195 200 205

Arg Asn Asn Gln Asp Leu Pro Arg Trp Ser Ala Met Pro Gln Gly Ala  
210 215 220

Pro Arg Lys Leu Ile Trp Met Gln Asn Xaa  
225 230

<210> 125

<211> 54  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (54)  
 <223> Xaa equals stop translation

<400> 125  
 Met Gln Gly Val Leu Phe Gly Phe Val Trp Leu Phe Ser Phe Leu Trp  
           1                  5                  10                  15  
 Gln Glu Asn Lys Ser Ser Ala Ser Pro Ser Thr Leu Ala Lys Ser Gly  
                   20                  25                  30  
 Ser Pro Cys Pro Val Ser Ile Pro Trp Met Pro Gly Val Leu Val Arg  
           35                  40                  45  
 Phe Phe Thr Leu Leu Xaa  
           50

<210> 126  
 <211> 82  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (44)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (82)  
 <223> Xaa equals stop translation

<400> 126  
 Met Arg Met Arg Val Ala Val Ala Pro Arg Pro His Gln His Leu Val  
           1                  5                  10                  15  
 Val Ser Val Ser Trp Ile Leu Ala Ile Leu Ile Ser Val Ser Gly Tyr  
                   20                  25                  30  
 His Cys Phe His Leu Gln Phe Ser Tyr Met Val Xaa Asn Ile Phe Pro  
           35                  40                  45  
 His Val Tyr Leu Ser Ser Ala Tyr Leu Leu Arg Pro Val Ile Cys Ser  
           50                  55                  60  
 Asp Leu Leu Pro Val Phe Val Cys Leu His Val Cys Leu Cys Leu Ile  
           65                  70                  75                  80  
 Phe Xaa

<210> 127  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals stop translation

<400> 127  
 Met Gly Trp Glu Ala Ala Leu Ala Leu Val Ser Ala Val Phe Phe  
           1                  5                  10                  15  
 Pro Trp Cys Thr Ile Gln Arg Pro Asp Val Gly Thr Thr Ser Pro Gly  
                   20                  25                  30  
 Gly Leu Glu Arg Arg Ser Lys Gly Phe Xaa  
           35                  40

<210> 128  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (66)  
 <223> Xaa equals stop translation

<400> 128  
 Met Thr Phe Met Ile Leu Lys Phe Phe Phe Leu Cys Gly Phe Val Leu  
           1                  5                  10                  15  
 Asn Arg Leu Ile Ala Arg Gln Leu Ala Lys Ile His Ala Ile His Ala  
                   20                  25                  30  
 His Asn Gly Trp Ile Pro Lys Ser Asn Leu Trp Leu Lys Met Gly Lys  
           35                  40                  45  
 Tyr Phe Ser Leu Ile Pro Thr Gly Phe Ala Asp Glu Asp Ile Asn Lys  
           50                  55                  60  
 Arg Xaa  
       65

<210> 129  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 129

Met Ile Val Asn His Phe Ser Phe Leu Phe Cys Trp Ile Val Phe Cys  
 1 5 10 15

Phe Leu Leu Gln His Ser Cys Phe Cys Cys Ala Tyr Phe Trp Ser Phe  
 20 25 30

Asp Ser Leu Cys His Cys Phe Leu Ser His Thr Pro Leu Arg Phe Thr  
 35 40 45

Gln Xaa  
 50

&lt;210&gt; 130

&lt;211&gt; 227

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (227)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 130

Met Glu Thr Val Val Ile Val Ala Ile Gly Val Leu Ala Thr Ile Phe  
 1 5 10 15

Leu Ala Ser Phe Ala Ala Leu Val Leu Val Cys Arg Gln Arg Tyr Cys  
 20 25 30

Arg Pro Arg Asp Leu Leu Gln Arg Tyr Asp Ser Lys Pro Ile Val Asp  
 35 40 45

Leu Ile Gly Ala Met Glu Thr Gln Ser Glu Pro Ser Glu Leu Glu Leu  
 50 55 60

Asp Asp Val Val Ile Thr Asn Pro His Ile Glu Ala Ile Leu Glu Asn  
 65 70 75 80

Glu Asp Trp Ile Glu Asp Ala Ser Gly Leu Met Ser His Cys Ile Ala  
 85 90 95

Ile Leu Lys Ile Cys His Thr Leu Thr Glu Lys Leu Val Ala Met Thr  
 100 105 110

Met Gly Ser Gly Ala Lys Met Lys Thr Ser Ala Ser Val Ser Asp Ile  
 115 120 125



Ile Val Val Ala Lys Arg Ile Ser Pro Arg Val Asp Asp Val Val Lys  
 130 135 140

Ser Met Tyr Pro Pro Leu Asp Pro Lys Leu Leu Asp Ala Arg Thr Thr  
 145 150 155 160

Ala Leu Leu Leu Ser Val Ser His Leu Val Leu Val Thr Arg Asn Ala  
 165 170 175

Cys His Leu Thr Gly Gly Leu Asp Trp Ile Asp Gln Ser Leu Ser Ala  
 180 185 190

Ala Glu Glu His Leu Glu Val Leu Arg Glu Ala Ala Leu Ala Ser Glu  
 195 200 205

Pro Asp Lys Gly Leu Pro Gly Pro Glu Gly Phe Leu Gln Glu Gln Ser  
 210 215 220

Ala Ile Xaa  
 225

<210> 131  
 <211> 118  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (118)  
 <223> Xaa equals stop translation

<400> 131  
 Met Gln Arg Ile Ala Ser Leu Leu Thr Leu Leu Thr Gln Leu Thr Leu  
 1 5 10 15

Ala Ala Gly Ser Thr Pro Ala Glu Thr Ile Ser Asp Ser Ala Glu Ala  
 20 25 30

Ser Leu Ser Ala Thr Pro Ser Leu Val Thr Trp Thr Gln Val Ser Gly  
 35 40 45

Leu Gln Pro Leu Val Glu Pro Cys Leu Arg Gln Thr Leu Lys Leu Leu  
 50 55 60

Ser Arg Pro Glu Met Trp Arg Ala Val Gly Pro Val Pro Val Ala Cys  
 65 70 75 80

Leu Leu Phe Leu Gly Ala Tyr Tyr Gln Ala Trp Ser Gln Gln Pro Ser  
 85 90 95

Ser Cys Pro Glu Asp Trp Leu Gln Asp Met Glu Arg Leu Ser Glu Ser  
 100 105 110

Cys Cys Cys His Cys Xaa

115

&lt;210&gt; 132

&lt;211&gt; 306

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (180)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (197)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (306)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 132

Met	Ser	Glu	Asp	Arg	Pro	Met	Leu	Gln	Phe	Leu	Leu	His	Thr	Ser	Phe
1				5					10					15	

Leu	Ser	Pro	Leu	Phe	Ile	Leu	Trp	Leu	Trp	Thr	Lys	Pro	Ile	Ala	Arg
			20					25						30	

Asp	Phe	Leu	His	Gln	Pro	Pro	Phe	Gly	Glu	Thr	Arg	Phe	Ser	Leu	Leu
			35				40					45			

Ser	Asp	Ser	Ala	Phe	Asp	Ser	Gly	Arg	Leu	Trp	Leu	Leu	Val	Val	Leu
	50					55					60				

Cys	Leu	Leu	Arg	Leu	Ala	Val	Thr	Arg	Pro	His	Leu	Gln	Ala	Tyr	Leu
65					70					75					80

Cys	Leu	Ala	Lys	Ala	Arg	Val	Glu	Gln	Leu	Arg	Arg	Glu	Ala	Gly	Arg
				85					90					95	

Ile	Glu	Ala	Arg	Glu	Ile	Gln	Gln	Arg	Val	Val	Arg	Val	Tyr	Cys	Tyr
			100					105					110		

Val	Thr	Val	Val	Ser	Leu	Gln	Tyr	Leu	Thr	Pro	Leu	Ile	Leu	Thr	Leu
			115				120					125			

Asn	Cys	Thr	Leu	Leu	Leu	Lys	Thr	Leu	Gly	Gly	Tyr	Ser	Trp	Gly	Leu
			130			135					140				

Gly	Pro	Ala	Pro	Leu	Leu	Ser	Pro	Arg	Pro	Ile	Leu	Ser	Gln	Arg	Cys
145					150					155					160

Pro	His	Arg	Leu	Trp	Gly	Gly	Arg	Ser	Pro	Ala	Asp	Cys	Ser	Ala	Asp
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

165										170					175					
Cys	Arg	Gly	Xaa	Gly	Trp	Pro	Ala	Tyr	Ser	Pro	Leu	Pro	Pro	Trp	Arg					
			180					185					190							
Pro	Gly	Leu	Pro	Xaa	Leu	Val	Asp	Gly	Cys	Leu	Pro	Ala	Ala	Arg	Gln					
		195					200					205								
Pro	Phe	Arg	Pro	Leu	Leu	Pro	Pro	Ala	Leu	Gly	Arg	Leu	Leu	Ala	Ala					
	210					215					220									
Cys	Arg	Pro	Ser	Trp	Gly	Pro	Glu	Val	Cys	Ser	Trp	Gly	Ser	Gly	Thr					
225					230					235					240					
Leu	Ala	Cys	Pro	Leu	Cys	Leu	Arg	Pro	Arg	Val	Pro	Ser	Cys	Lys	Val					
				245					250					255						
Gly	Pro	Asp	Ser	Pro	Ala	Phe	Pro	Ser	Pro	Gln	Cys	Leu	Thr	Arg	Gly					
			260					265					270							
Pro	Pro	Trp	Thr	Pro	Ser	Phe	Cys	Leu	Arg	Thr	Val	Ser	Pro	Gly	Pro					
		275					280					285								
Ser	Ser	Met	Arg	Val	Pro	Arg	Pro	Leu	Ser	Pro	Lys	Arg	Met	Cys	Gln					
	290					295					300									
Val	Xaa																			
305																				

```
<210> 133
<211> 45
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (45)
<223> Xaa equals stop translation
```

```
<400> 133
Met Ser Tyr Ser Leu Phe Leu Ala Leu Leu Ser Phe Ala Ser Ala Ile
  1             5              10             15
```

Leu Phe Val Ala Gly Thr Ile Ala Gly Thr Gly Gly Leu Ser Phe His  
20 25 30

Gly Ile Ala Thr Ile Phe Val Leu Thr Gly Lys Trp Xaa  
35 40 45

```
<210> 134
<211> 44
<212> PRT
<213> Homo sapiens
```

<220>  
<221> SITE  
<222> (6)  
<223> Xaa equals any of the naturally occurring L-amino acids

<220>  
<221> SITE  
<222> (44)  
<223> Xaa equals stop translation

<400> 134  
Met Gly Arg Leu Gly Xaa Gln Cys Leu Leu Phe Leu Ala Phe Lys Ala  
1 5 10 15  
Ile Ser Gly Val Phe Phe Leu Phe Trp Arg Pro Ala Asp Ser Thr Glu  
20 25 30  
Arg Asn Thr Gln Ser Trp Asp Phe Pro Pro Leu Xaa  
35 40

<210> 135  
<211> 50  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (50)  
<223> Xaa equals stop translation

<400> 135  
Met Gly Val Gly Val Leu Arg Ile Leu Leu Ser Cys Leu Gly Glu Ala  
1 5 10 15  
Ala Pro Lys Ser Ala Gly Thr Ser Leu Glu Ser Ala Lys Glu Cys Trp  
20 25 30  
Ser Ala Ala Thr Leu Leu Val Leu Cys Val Leu Cys Gln Leu Gln His  
35 40 45  
Gly Xaa  
50

<210> 136  
<211> 81  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (81)  
<223> Xaa equals stop translation

&lt;400&gt; 136

Met Glu Ser Leu Pro Glu Asn Lys Pro Leu Val Trp Ser Leu Ala Val  
 1 5 10 15  
 Ser Leu Leu Ala Ile Ile Gly Leu Leu Leu Gly Ser Ser Pro Asp Phe  
 20 25 30  
 Asn Ser Gln Phe Gly Leu Val Asp Ile Pro Val Glu Phe Lys Leu Val  
 35 40 45  
 Ile Ala Gln Val Leu Leu Leu Asp Phe Cys Leu Ala Leu Leu Ala Asp  
 50 55 60  
 Arg Val Leu Gln Phe Phe Leu Gly Thr Pro Lys Leu Lys Val Pro Ser  
 65 70 75 80

Xaa

&lt;210&gt; 137

&lt;211&gt; 277

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (94)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (103)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (277)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 137

Met Ile His Val Asn Arg Asn Ile Met Asp Phe Lys Leu Phe Leu Val  
 1 5 10 15  
 Phe Val Ala Gly Val Phe Leu Phe Phe Tyr Ala Arg Thr Leu Glu Ser  
 20 25 30  
 Lys Pro Tyr Phe Leu Leu Leu Leu Gly Asn Cys Ala Arg Cys Ser Asn  
 35 40 45  
 Asp Ile Val Phe Val Leu Leu Leu Val Lys Arg Phe Ile Arg Ser Ile  
 50 55 60  
 Ala Pro Phe Gly Ala Leu Met Val Gly Cys Trp Phe Ala Ser Val Tyr

65		70		75		80
Ile Val Cys Gln Leu Met Glu Asp Leu Lys Trp Leu Trp Xaa Glu Asn						
		85		90		95
Arg Ile Tyr Val Ser Gly Xaa Val Leu Ile Val Gly Phe Phe Ser Phe						
		100		105		110
Val Val Cys Tyr Lys His Gly Pro Leu Ala His Asp Arg Ser Arg Ser						
		115		120		125
Leu Leu Met Trp Met Leu Arg Leu Leu Ser Leu Val Leu Val Tyr Ala						
		130		135		140
Gly Val Ala Val Pro Gln Phe Ala Tyr Ala Ala Ile Ile Leu Leu Met						
		145		150		155
Ser Ser Trp Ser Leu His Tyr Pro Leu Arg Ala Cys Ser Tyr Met Arg						
		165		170		175
Trp Lys Met Glu Gln Trp Phe Thr Ser Lys Glu Leu Val Val Lys Tyr						
		180		185		190
Leu Thr Glu Asp Glu Tyr Arg Glu Gln Ala Asp Ala Glu Thr Asn Ser						
		195		200		205
Ala Leu Glu Glu Leu Arg Arg Ala Cys Arg Lys Pro Asp Phe Pro Ser						
		210		215		220
Trp Leu Val Val Ser Arg Leu His Thr Pro Ser Lys Phe Ala Asp Phe						
		225		230		235
Val Leu Gly Gly Ser His Leu Ser Pro Glu Glu Ile Ser Leu His Glu						
		245		250		255
Glu Gln Tyr Gly Leu Gly Gly Ala Phe Leu Glu Glu Gln Leu Phe Asn						
		260		265		270
Pro Ser Thr Ala Xaa						
		275				

&lt;210&gt; 138

&lt;211&gt; 57

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 138

Met Cys Gln Thr Leu Pro Ala Arg Leu Arg Ala Gln Cys Ile Ser Ser
1 5 10 15

Leu Leu Phe Leu Leu Met Gly Leu Leu Ala Met Thr Gly Glu Arg Asn  
20 25 30

Gln Gly Thr His Tyr Tyr Glu Phe Ser Gly Phe Ile Phe Lys Ser Gln  
35 40 45

Met Met Trp Ser Ile Lys Pro Asn Xaa  
50 55

```
<210> 139
<211> 71
<212> PRT
<213> Homo sapiens
```

```
<220>  
<221> SITE  
<222> (71)  
<223> Xaa equals stop translation
```

```

<400> 139
Met Tyr Leu Trp Phe Ser Phe Ser Thr Val Gly Leu Cys Gly Cys Cys
  1             5             10             15
Leu Leu Tyr Arg Ala Cys Gly Phe Ile Trp Tyr Leu Leu Leu Leu Gly
      20             25             30
His Ser Ser Thr Asn Ser Leu Gln Asp Gly Gly Ala Glu Arg Pro Glu
      35             40             45
His Pro Trp Ala His Val Arg Tyr Ser Cys Arg Arg Glu Leu Ser Phe
      50             55             60
Trp Phe Tyr Val Phe Asn Xaa
  65             70

```

```
<210> 140
<211> 63
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (63)
<223> Xaa equals stop translation
```

```

<400> 140
Met Glu Pro Glu Ser Trp Ala Leu Cys Leu Leu Leu Phe Leu Gly Thr
  1                      5                      10                      15
Ala Leu Gly Tyr Pro Pro Leu Pro Arg His Ser Ser Lys Cys Glu Ile
      20                      25                      30

```

Leu Glu Val Arg Leu His Leu Leu Pro Leu Leu Ile Asn Ile Gly Met  
                   35                                  40                                  45

Met Ser Pro Val Ala Ser Pro Phe Val Cys Ser Ile Thr Gly Xaa  
           50                                  55                                  60

<210> 141  
 <211> 89  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (89)  
 <223> Xaa equals stop translation

<400> 141  
 Met Leu Phe Leu Ser Ala Ser Ile Cys Thr Ser Ala Leu Phe Leu Cys  
   1                                  5                                  10                                  15

Leu Ser Arg Leu Thr Ile Ser Ala Pro His Pro Ala Trp Trp Gly Arg  
                   20                                  25                                  30

Met Pro Thr His Thr Ser Pro Gly His Leu Leu Glu Leu Gln Pro Arg  
                   35                                  40                                  45

Gly Met Thr Glu Ser Ile Leu Phe Ser Ile Ser Ala Leu Val Ser Asn  
           50                                  55                                  60

Ser Trp Gly Lys Met Thr Gln Leu Thr Ser Gly Ser His Ser Trp Ser  
   65                                  70                                  75                                  80

Ser Gly Leu Gln Asn Phe Gln Ala Xaa  
                                   85

<210> 142  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (46)  
 <223> Xaa equals stop translation

<400> 142  
 Met Arg Pro Val Cys Ser Leu Gly Trp Ala Gly Trp Pro Gly Leu Val  
   1                                  5                                  10                                  15

Cys Gly Leu Arg Ala Leu Leu Gly Pro Ser Leu Phe Pro Val Thr Phe  
                   20                                  25                                  30

Gly Ala Thr Glu Ala Val His Ser Leu Asp Val Cys Ser Xaa



35

40

45

&lt;210&gt; 143

&lt;211&gt; 56

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (56)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 143

Met Val Asn Glu Lys Glu Ala Arg Thr Gly Ser Pro Lys Ser Trp Leu  
 1 5 10 15

Leu Cys Leu Ala Leu Leu Leu Ile Lys Tyr Val Thr Phe Cys Lys Pro  
 20 25 30

Tyr Leu Thr Lys Pro Tyr Phe Leu His Leu Ser Val Leu Asp Gln Leu  
 35 40 45

Ser Pro Gly Thr Pro Leu Asp Xaa  
 50 55

&lt;210&gt; 144

&lt;211&gt; 77

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (77)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 144

Met Phe Ile Ala Ile Tyr Phe Lys Ala Phe His Gly Ser Phe Gln Leu  
 1 5 10 15

Cys Thr Trp Leu Val Ile Met Ile Val Ile Leu Gly Gln Ser Phe Ser  
 20 25 30

Ala Leu Ala Leu Leu Thr Phe Trp Leu Ile Leu Cys Cys Arg Gly Cys  
 35 40 45

Pro Val His Cys Arg Val Phe Ser Ser Ile Pro Asp Leu Tyr Leu Leu  
 50 55 60

Asn Ala Arg Ser Asn Thr Val Pro Pro Ala Gln Leu Xaa  
 65 70 75

&lt;210&gt; 145

<211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 145  
 Met Phe Phe Leu Ser Met Phe Leu His Ile Val Leu Leu His Cys Gly  
           1                  5                  10                  15  
 Asn Ser Phe Tyr Lys Ile Cys His Ser Trp Asp Tyr Ala Ala Leu Gln  
                   20                  25                  30  
 Glu Ser Thr Arg Phe Tyr Ser Asn Ser Tyr Xaa  
                   35                  40

<210> 146  
 <211> 102  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (67)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (102)  
 <223> Xaa equals stop translation

<400> 146  
 Met Glu Leu Glu Arg Cys Ser Val Val Leu Cys Ile Leu Ala Asn Leu  
           1                  5                  10                  15  
 Ala Val Leu Arg Ala Leu Phe Leu Pro Cys Ile Ile Phe His Cys Val  
                   20                  25                  30  
 Ser Asp Ser Arg Ser Val Asn Arg Glu Thr Lys Val Lys Phe Val His  
           35                  40                  45  
 Thr Ser Val His Gly Val Gly His Ser Phe Val Gln Ser Ala Phe Lys  
           50                  55                  60  
 Ala Phe Xaa Leu Val Pro Pro Glu Ala Val Pro Glu Gln Lys Asp Pro  
           65                  70                  75                  80  
 Asp Pro Glu Phe Pro Thr Val Lys Tyr Pro Asn Pro Glu Glu Gly Lys  
                   85                  90                  95  
 Gly Val Leu Val Thr Xaa

100

&lt;210&gt; 147

&lt;211&gt; 134

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (134)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 147

Met	Arg	Val	Pro	Leu	Val	Leu	Ser	Trp	Ala	Phe	Val	Leu	Val	Gly	Phe
1				5					10					15	

Ser	Gly	Val	Tyr	Leu	Ala	Ser	Glu	Ser	Phe	Trp	Phe	Pro	Pro	Ser	Leu
			20					25					30		

Cys	Asp	Leu	Thr	Ser	Pro	Pro	Gly	Leu	His	Leu	Trp	Lys	Phe	Ile	Arg
		35					40					45			

Asp	Leu	Val	Ser	Met	Glu	Glu	Leu	Thr	Asp	Ser	Ala	Arg	Glu	Met	Gly
	50					55					60				

Tyr	Trp	Met	Met	Val	Phe	Ser	Leu	Lys	Ala	Met	Phe	Pro	Val	Ser	Ser
65					70					75					80

Gly	Cys	Phe	Gln	Glu	Arg	Gln	Glu	Thr	Asn	Lys	Ser	Leu	Thr	Leu	Leu
			85						90					95	

Arg	Cys	Ser	Gln	Arg	Asp	Thr	Ser	Pro	Leu	Met	Asp	Gly	Gln	Thr	Trp
		100						105					110		

Ala	Arg	Val	Arg	Val	Thr	Lys	Pro	Pro	Thr	Thr	Ala	Thr	Ala	Ala	Tyr
		115					120					125			

Asn	Arg	His	Ile	Arg	Xaa
					130

&lt;210&gt; 148

&lt;211&gt; 50

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (50)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 148

Met	Lys	Ser	Leu	Phe	Cys	Ile	Tyr	Phe	Leu	Arg	Trp	Pro	Met	Gly	Leu
1				5					10					15	

Ser Trp Gly Glu Thr Phe Ile Leu Leu Arg Asp Ser Leu Ala Ile Asn  
                   20                  25                  30  
 Phe Gln Ser Phe Ser Lys Ala Ala Ser Gly Asp Ile Phe Gly Cys His  
           35                  40                  45  
 Asp Xaa  
       50

<210> 149  
 <211> 64  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (6)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (64)  
 <223> Xaa equals stop translation

<400> 149  
 Met Ser Cys Gly Leu Xaa Phe Gly Pro Trp Phe Val Pro Met Leu Leu  
       1                  5                  10                  15  
 Met Ser His Ser Leu Leu Pro Ser Trp Ser Gly Leu Trp Val Thr Thr  
           20                  25                  30  
 Trp Asn Gly Ser Ser Gly Glu Arg Thr Pro Ser Pro Trp Arg Arg Lys  
           35                  40                  45  
 Arg Ala Ser Gln Ser Ala Gly Arg Ile Ala Ser Trp Met Ser Phe Xaa  
       50                  55                  60

<210> 150  
 <211> 75  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (59)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE

&lt;222&gt; (75)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 150

Met	Leu	Ser	Ser	Pro	Asn	Leu	Ala	Ala	Ser	Leu	Leu	Cys	Leu	Trp	His
1				5					10					15	

Ser	Gly	Ser	Ala	Thr	Asn	Trp	Ala	Pro	Pro	Cys	Ala	Gly	Met	Trp	Ala
			20					25					30		

Ser	Arg	Cys	Gly	Trp	Lys	Val	Ser	Pro	His	Pro	Glu	Ala	Gly	Pro	Cys
		35					40					45			

Ser	Ser	Ala	Leu	Trp	Val	Ser	Cys	Cys	Val	Xaa	Ala	Glu	Gln	Pro	Gln
	50					55				60					

Pro	Gly	Gly	Arg	Glu	Pro	Arg	His	Arg	Gly	Xaa
65					70					75

&lt;210&gt; 151

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 151

Met	Pro	His	Ile	Ser	Phe	Cys	Leu	Gly	Thr	Pro	Tyr	Val	Val	Ala	Val
1				5					10					15	

Tyr	Leu	Pro	Ala	Trp	Ile	Val	Met	Leu	Leu	Leu	Pro	Gly	Val	Arg	Pro
			20				25						30		

Tyr	Ser	Ser	Leu	Gln	Ala	Leu	Lys	His	Pro	Ser	Cys	Ser	Ser	Ser	Ser
		35					40					45			

Val	Cys	Ala	Pro	Tyr	Met	Xaa
50					55	

&lt;210&gt; 152

&lt;211&gt; 58

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (58)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 152

92

Met Gly Leu Asn Ile Ser Pro Trp Cys Phe Leu Ala Ile Leu Thr Cys  
 1 5 10 15  
 Ala Ile Ser Ala Ala Phe Ile Ser Val Gly Val Val Cys Trp Leu Leu  
 20 25 30  
 Phe Leu Ile Ser His Arg Ser Ser Lys Asn Leu Arg Lys Ser Arg Val  
 35 40 45  
 Arg Gly Val Trp Glu Asn Glu Glu Ile Xaa  
 50 55

<210> 153  
 <211> 53  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (53)  
 <223> Xaa equals stop translation

<400> 153  
 Met Ala Tyr Val Leu Ala Val Leu Cys Phe Lys Ser Leu Trp Ala Leu  
 1 5 10 15  
 Phe Lys Pro Asn Lys Gln Leu Ile Glu Phe Leu Leu Met Val Lys Val  
 20 25 30  
 Val Lys Ile Pro Leu Cys Tyr Leu Arg Gln Leu Leu Gly Gly Ile Lys  
 35 40 45  
 Thr Pro Arg Val Xaa  
 50

<210> 154  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (51)  
 <223> Xaa equals stop translation

<400> 154  
 Met Asp Gly Gly Pro Gly Ala Phe Ser Arg Ala Trp Val Leu Gln Ile  
 1 5 10 15  
 Pro Trp Leu Leu Leu Ser Gly Gly Asn Phe Ala Leu Cys Glu Pro Arg  
 20 25 30  
 Pro Cys Pro Ser Ala Gly His Pro Trp Gln Glu Ala Gly Leu Pro Ser

35

40

45

Ser Pro Xaa  
50

&lt;210&gt; 155

&lt;211&gt; 67

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (67)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 155

Met Pro Phe Leu Ser Val Trp Phe Phe Asn Leu Gly Leu Ile Phe Gly  
1 5 10 15

Val Glu Ser Phe Val Leu Arg Ala Val Leu Phe Ile Ala Gly Cys Ser  
20 25 30

Ala Thr Ser Gln Met Glu Ala Ala Ser Pro Tyr Pro Ala Val Thr Lys  
35 40 45

Arg Lys Lys Asn Val Ser Xaa His Cys Gln Ile Ser Ser Gly Gly Ala  
50 55 60

Pro Gly Xaa  
65

&lt;210&gt; 156

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 156

Met Leu Leu Lys Arg Asn Leu Leu Ile Leu Ile Leu Phe Leu Val Thr  
1 5 10 15

Cys Phe Asn Phe Val Ser Phe Phe Phe Phe Pro Trp Lys Leu Leu Gly  
20 25 30

Ser Pro Phe Tyr Pro Cys Ser Leu Arg Ser Asp Asn Asp Gly Cys Val  
                   35                                  40                                  45

Xaa

<210> 157  
 <211> 61  
 <212> PRT  
 <213> Homo sapiens

<400> 157  
 Met Gly Ser Phe Leu His Pro Gln Trp His Leu Leu Ile Thr Phe Cys  
   1                                  5                                  10                                  15

Ala Val Leu Gly Lys Gly Leu His Ser Asp Pro Ser Arg Pro Phe Glu  
                   20                                  25                                  30

His Gly Gly Ala Leu Gly Lys Val Pro Arg Gly Arg Ser Thr Leu Leu  
                   35                                  40                                  45

Ser Lys Glu Val Leu Leu Lys Lys Lys Lys Lys Lys Arg  
           50                                  55                                  60

<210> 158  
 <211> 118  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (113)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (118)  
 <223> Xaa equals stop translation

<400> 158  
 Met Leu Leu Trp Trp Gln Cys Leu Cys Cys His Ala Val Leu Glu Pro  
   1                                  5                                  10                                  15

Ala Ala Thr Ala Met Pro Glu Asp Ala Ala Pro Ser Ser Leu Pro Val  
                   20                                  25                                  30

Pro Pro Asn Met Thr Ser Ser Arg Phe His Tyr Phe Trp Thr Leu Leu  
                   35                                  40                                  45

Gln Ile Lys Leu Thr Gln Phe Tyr Ser Lys Pro Arg Ser Leu Ser Ala  
           50                                  55                                  60

Thr Pro Glu Lys Asn Ile Gly Leu Gln Glu Pro Glu Arg Arg Glu Arg



```
<210> 159
<211> 151
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (151)
<223> Xaa equals stop translation
```

```

<400> 159
Met Leu Ala Val Leu Ala Phe Pro Val Gly Val Phe Val Val Ala Val
  1             5             10             15

Phe Trp Ile Ile Tyr Ala Tyr Asp Arg Glu Met Ile Tyr Pro Lys Leu
      20             25             30

Leu Asp Asn Phe Ile Pro Gly Trp Leu Asn His Gly Met His Thr Thr
      35             40             45

Val Leu Pro Phe Ile Leu Ile Glu Met Arg Thr Ser His His Gln Tyr
  50             55             60

Pro Ser Arg Ser Ser Gly Leu Thr Ala Ile Cys Thr Phe Ser Val Gly
  65             70             75             80

Tyr Ile Leu Trp Val Cys Trp Val His His Val Thr Gly Met Trp Val
      85             90             95

Tyr Pro Phe Leu Glu His Ile Gly Pro Gly Ala Arg Ile Ile Phe Phe
      100             105             110

Gly Ser Thr Thr Ile Leu Met Asn Phe Leu Tyr Leu Leu Gly Glu Val
      115             120             125

Leu Asn Asn Tyr Ile Trp Asp Thr Gln Lys Ser Met Glu Glu Glu Lys
      130             135             140

Glu Lys Pro Lys Leu Glu Xaa
145             150

```

<210> 160

<211> 92  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (92)  
 <223> Xaa equals stop translation

<400> 160  
 Met Gly Asp Lys Leu Gly Met Ala Arg Ala Pro Ser Val Ala Leu Ala  
   1                  5                  10                  15  
 Gln Leu Trp Leu Ile Cys Leu Cys Pro Glu Ser Leu Ala Ser Phe Val  
           20                  25                  30  
 Gln Ala Val Pro Trp Lys Val Leu Gln Pro Ser Ser Asn Arg Ser Thr  
           35                  40                  45  
 Asp Cys Ser Pro His Met Arg Pro Thr Cys Glu Thr Leu Gly Ser Arg  
       50                  55                  60  
 Lys Ala Gln Asp Leu Val Leu Asp Thr Met Cys Leu Ser Thr Asp Asp  
   65                  70                  75                  80  
 Cys Gln Gly Leu Ile Cys Arg Gly His Arg Ser Xaa  
                   85                  90

<210> 161  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (42)  
 <223> Xaa equals stop translation

<400> 161  
 Met Gln Val Ala Cys Val Met Lys Val Ser Ala Gln Trp Val Cys Phe  
   1                  5                  10                  15  
 Phe Val Val Phe Ser Pro Leu Cys Ser Ser Val Lys Cys Ala Ser Ser  
           20                  25                  30  
 Gly Gln Asn Arg Gly Arg Gly Asp Gln Xaa  
       35                  40

<210> 162  
 <211> 78  
 <212> PRT  
 <213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (78)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 162

Met Met Leu Gln Ile Ile His Leu Asn Thr Leu Ile Lys Phe Phe Gln  
1 5 10 15

Cys Leu Lys Leu Phe Leu His Gly Thr Ala Gly Ser Gly Gln Lys Cys  
20 25 30

Leu Ala Tyr Lys Phe Ser Gln Phe Pro Ser Ile Ile Pro Ala Ala His  
35 40 45

Lys Lys Val His His Leu Leu Ser Pro Lys Cys Leu Pro Thr Glu Cys  
50 55 60

Ser Gln Ala Asp Asn Ser Ser Trp Asp Ser Ala Val Trp Xaa  
65 70 75

&lt;210&gt; 163

&lt;211&gt; 55

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (55)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 163

Met Lys Arg Leu Trp Cys Leu Ser Trp Val Pro Gly Leu Gln Gly Ser  
1 5 10 15

Pro Ser Val Leu Ser Ser Val Phe Phe Ser Val Phe Lys Pro Gln Leu  
20 25 30

His Trp Thr Cys Ser Gln Val Ser Ser His Trp His Pro Pro Cys Leu  
35 40 45

Phe Ile Leu Phe Ser Gly Xaa  
50 55

&lt;210&gt; 164

&lt;211&gt; 90

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (90)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 164

Met Lys Phe Leu Leu Ala Ala Leu Val Leu Ser Leu Ile Leu Pro Arg  
 1 5 10 15

Ser Ser Gln Tyr Ile Lys Trp Ile Val Ser Ala Gly Leu Ala Gln Val  
 20 25 30

Ser Glu Phe Ser Phe Val Leu Gly Ser Arg Ala Arg Arg Ala Gly Val  
 35 40 45

Ile Ser Arg Glu Val Tyr Leu Leu Ile Leu Ser Val Thr Thr Leu Ser  
 50 55 60

Leu Leu Leu Ala Pro Val Leu Trp Arg Ala Ala Ile Thr Arg Cys Val  
 65 70 75 80

Pro Arg Pro Glu Arg Arg Ser Ser Leu Xaa  
 85 90

&lt;210&gt; 165

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (45)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 165

Met Phe Val Trp His Leu Lys Val Met Val Met Phe Ile Ile Leu Tyr  
 1 5 10 15

Phe Ala Tyr Cys Glu Ser Asn Phe His Ser Val Leu Ser Val Ser Lys  
 20 25 30

Pro Leu Leu Lys Ile Leu Phe Leu Pro Arg Asn Leu Xaa  
 35 40 45

&lt;210&gt; 166

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (45)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 166

Met Thr Pro Gly Cys Ser Val Pro Phe Leu Leu Cys Trp Leu Phe Ala  
 1 5 10 15

Leu Met Met Gln Glu Lys Trp Gly Gly Val Lys Ser Leu Val Ser Tyr  
                   20                                  25                                  30

His Tyr Ser Arg Gln Trp His Gln Thr Val Val Val Xaa  
           35                                  40                                  45

<210> 167  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (66)  
 <223> Xaa equals stop translation

<400> 167  
 Met Ser Ile Ala Leu Arg Ile Asn Arg Leu His Phe Trp Val Leu Leu  
   1                                  5                                  10                                  15

Phe Phe Phe Phe Phe Ala Gln Leu Ser Leu Ser Val Asp Leu His Gly  
                   20                                  25                                  30

Thr Ser Tyr Ser Leu Lys Ser Leu Ser Tyr Leu Thr Ile Phe Leu Asp  
           35                                  40                                  45

Leu Glu Lys Leu Asp Val Gly Pro Tyr Glu Lys Ile Ile Arg Asn Gln  
           50                                  55                                  60

Ile Xaa  
   65

<210> 168  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals stop translation

<400> 168  
 Met Gln Leu Thr Leu Gly Gly Ala Ala Val Gly Ala Gly Ala Val Leu  
   1                                  5                                  10                                  15

Ala Ala Ser Leu Leu Trp Ala Cys Ala Val Gly Leu Tyr Met Gly Gln  
           20                                  25                                  30

Leu Glu Leu Asp Val Glu Leu Val Pro Glu Asp Asp Gly Thr Ala Ser  
           35                                  40                                  45

100

Ala Glu Gly Pro Asp Glu Ala Gly Arg Pro Pro Pro Glu Xaa  
 50 55 60

&lt;210&gt; 169

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 169

Met His Thr Ala Lys Met Ser Leu Leu Asn Ser Val Cys Leu Leu Val  
 1 5 10 15

Leu Ser Ile Trp Tyr Val Val Lys Phe Pro Met Met Arg Asp Ser Thr  
 20 25 30

Ile Asn Val Pro Tyr Leu Leu Arg Leu Lys Ala Ile Thr Thr Xaa  
 35 40 45

&lt;210&gt; 170

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (69)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (106)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 170

Met Ser Gly Leu Ala Ala Ala Ala His Val Phe Arg Val Cys Leu Phe  
 1 5 10 15

Pro Leu Ser Trp Gly Ser Ser Lys Thr Thr Phe Ile His Gly Leu Ser  
 20 25 30

Ser Tyr Ile Ala Thr Pro Val Leu Asn Ser Ile Phe Ser Ser Trp Lys  
 35 40 45

Ser Arg Arg Lys Asp Thr Trp Thr Cys Leu Leu His Arg Leu Ser Ala  
 50 55 60

Phe Pro Ile Ser Xaa Arg Arg Arg Asn Phe Ala Leu Phe Ser His Ser  
 65 70 75 80

Cys Val Cys Ile Arg Ser Ser Ser Asp Asp Val Gly Pro Thr Met Tyr  
                             85                            90                            95

Ser Phe Ser Val Pro Cys Arg Val Lys Xaa  
                             100                            105

<210> 171  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (45)  
 <223> Xaa equals stop translation

<400> 171  
 Met His Leu Leu Thr Leu Phe Ser Ser Gly Leu Ile Phe Leu Gly Cys  
       1                            5                            10                            15

Ser Thr Pro Leu Ser Phe Cys Asp Cys Leu Pro Ile Leu Leu Leu Trp  
                             20                            25                            30

Leu Glu Phe Pro Val Glu Thr Ser Gly Val Cys Ser Xaa  
                             35                            40                            45

<210> 172  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (47)  
 <223> Xaa equals stop translation

<400> 172  
 Met Ile Leu Lys His Tyr Ile Leu Thr Phe Ile Phe Leu Phe Ile Phe  
       1                            5                            10                            15

Leu Phe Phe Met Leu Asn Ile Leu His Ser Asn Ser Asn Leu Ile Asp  
                             20                            25                            30

Leu Leu Lys Gly Asn Ile Arg Phe Arg Leu Leu Asn Ser Met Xaa  
                             35                            40                            45

<210> 173  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

102

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (42)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 173

Met Ala Thr Leu Gln Ile Thr Thr Ala Met Lys Ile Thr Met Met Ile  
1 5 10 15

Thr Met Val Met Ile Ile Thr Thr Ile Val Glu Ala Met Lys Ile Pro  
20 25 30

Thr Thr Ala Met Met Met Ala Met Gln Xaa  
35 40

&lt;210&gt; 174

&lt;211&gt; 47

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (47)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 174

Met Glu Met Leu Ser Ser Lys Trp Ser Lys Arg Val Ala Ala Ser Leu  
1 5 10 15

Ala His Leu Ile Ser Leu Phe Ile Gly Leu Leu Phe Leu Leu Leu Gly  
20 25 30

Ser Ser Val Tyr Pro Gly Thr Glu Thr Leu Phe Pro Lys Ser Xaa  
35 40 45

&lt;210&gt; 175

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 175

Met Trp Pro Ser Leu Gly Arg Cys Cys Leu Phe Phe Cys Leu Leu Thr  
1 5 10 15

Asn Leu Thr Ser Cys His Thr Ser Gln Ile Thr Leu Cys Ser Arg Glu  
20 25 30

Thr Cys Val Trp Ser Arg Thr Thr Xaa



35

40

&lt;210&gt; 176

&lt;211&gt; 53

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (53)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 176

Met	Tyr	Leu	Met	Ser	Phe	Ser	Ile	His	Phe	Val	Lys	Ile	Ile	Cys	Met
1				5					10					15	

Cys	Thr	Ile	Leu	Val	Leu	Ser	Pro	Pro	Val	Leu	Leu	Lys	Tyr	Gln	Asp
			20					25					30		

Ser	Thr	Pro	Arg	Pro	Leu	Trp	Ser	Gln	Cys	Lys	Ile	Pro	Ile	Asn	Tyr
		35					40					45			

Leu	Lys	Gly	Lys	Xaa
				50

&lt;210&gt; 177

&lt;211&gt; 250

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (250)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 177

Met	Arg	Gly	Pro	Ser	Trp	Ser	Arg	Pro	Arg	Pro	Leu	Leu	Leu	Leu	Leu
1				5					10					15	

Leu	Leu	Leu	Ser	Pro	Trp	Pro	Val	Trp	Ala	Gln	Val	Ser	Ala	Arg	Ala
			20					25					30		

Ser	Pro	Ser	Gly	Ser	Leu	Gly	Ala	Pro	Asp	Cys	Pro	Glu	Val	Cys	Thr
		35					40					45			

Cys	Val	Pro	Gly	Gly	Leu	Pro	Ala	Val	Gly	Thr	Leu	Ala	Ala	Arg	Arg
	50					55					60				

Ala	Pro	Gly	Pro	Glu	Pro	Ala	Pro	Ala	Arg	Ala	Ala	Ala	Gly	Pro	Gln
65					70				75					80	

Pro	Arg	Pro	Cys	Ala	Ala	Ala	Arg	Cys	Leu	Arg	Gly	Ser	Gly	Arg	Ala
				85					90					95	

104

Thr Ala Pro Gly Pro Ala Arg Glu Arg Ala Ala Leu Gly Ala Cys Ala  
                   100                  105                  110  
 Ser Leu Leu Gly Pro Gly Arg Ala Ala Ala Gly Pro Glu Arg Gln  
                   115                  120                  125  
 Pro Ala Gly Ser Thr Gly Thr Arg Asp Phe Arg Ala Ala Ala Arg Ala  
                   130                  135                  140  
 Ala Gln Pro Leu Ile Gly Arg Gln Pro Ala Gly Ala Pro Gly Ala Arg  
                   145                  150                  155                  160  
 Gly Ala Arg Arg Ala Pro Ala Ala Ala Leu Thr Gln Pro Ala Gly Gln  
                   165                  170                  175  
 Arg Ala Gly Gly Thr Arg Ala Gly Ala Ala Gly Pro Pro Ala Arg Ser  
                   180                  185                  190  
 Arg Arg Ala Ala Pro Ala Arg Gln Pro Leu Gly Leu Arg Val Arg Ala  
                   195                  200                  205  
 Ala Pro Ala Leu Arg Leu Ala Ala Pro Ala Pro Ala Ala Arg Val Arg  
                   210                  215                  220  
 Gly Arg Asp Gly Ala Leu Arg Val Ala Gly Thr Pro Asp Ala Gln Pro  
                   225                  230                  235                  240  
 Pro Asp Cys Leu Phe Arg Arg Arg Leu Xaa  
                   245                  250

&lt;210&gt; 178

&lt;211&gt; 148

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (148)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 178

Met Leu Ala Gly Ala Gly Arg Pro Gly Leu Pro Gln Gly Arg His Leu  
   1                  5                  10                  15  
 Cys Trp Leu Leu Cys Ala Phe Thr Leu Lys Leu Cys Gln Ala Glu Ala  
                   20                  25                  30  
 Pro Val Gln Glu Glu Lys Leu Ser Ala Ser Thr Ser Asn Leu Pro Cys  
                   35                  40                  45  
 Trp Leu Val Glu Glu Phe Val Val Ala Glu Glu Cys Ser Pro Cys Ser  
                   50                  55                  60

105

Asn Phe Arg Ala Lys Thr Thr Pro Glu Cys Gly Pro Thr Gly Tyr Val  
 65 70 75 80

Glu Lys Ile Thr Cys Ser Ser Ser Lys Arg Asn Glu Phe Lys Ser Cys  
 85 90 95

Arg Phe Ser Phe Glu Trp Asn Asn Ala Tyr Phe Gly Ser Ser Lys Gly  
 100 105 110

Ala Val Val Cys Val Ala Leu Ile Phe Ala Cys Leu Val Ile Ile Arg  
 115 120 125

Gln Arg Gln Leu Asp Arg Lys Ala Leu Glu Lys Val Arg Lys Gln Ile  
 130 135 140

Glu Ser Ile Xaa  
 145

<210> 179  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (48)  
 <223> Xaa equals stop translation

<400> 179  
 Met Phe Met Cys Arg Leu Leu Leu Trp Ala Thr Gly Ala Tyr Gly Phe  
 1 5 10 15

Leu Gly Asp Asp Val Glu Tyr Thr Ser Val Leu Pro His Gln Lys Gly  
 20 25 30

Lys Glu Ala Trp Val Phe Ile Cys Gln Leu Pro Phe Ile Ile Gly Xaa  
 35 40 45

<210> 180  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (56)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE

&lt;222&gt; (57)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 180

Met Leu Gln Thr Leu Leu Cys Leu Trp Gln Tyr Thr Ser Ala Gln Val  
 1 5 10 15

Leu Lys Met Leu Cys Ile His Arg Gln Lys Trp Asp Asn Phe Trp Ala  
 20 25 30

Val Val Met Ile Asn Leu Leu Ile Arg Ile Gln Arg Leu Pro Phe Ser  
 35 40 45

Leu Pro Ile Ala Leu Arg Val Xaa Xaa  
 50 55

&lt;210&gt; 181

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (49)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 181

Met Pro Ser Glu Gly Arg Leu Val Leu Leu Ser Ala Phe Cys Pro Ala  
 1 5 10 15

Phe Phe Pro Pro Trp Val Leu Ser Gly Ser Phe Ala Phe Ser Leu Cys  
 20 25 30

Ala Glu Ser His Leu Asn Ser Ser His Arg Arg Ile Ala Val Trp Thr  
 35 40 45

Xaa

&lt;210&gt; 182

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (46)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 182

Met Val Gln Trp Lys Asn Trp Pro Glu Ser Leu Glu Val Trp Val Leu  
 1 5 10 15

107

Val Leu Ala Val Pro Leu Thr His Cys Asp Leu Gly Ile Leu Cys Cys  
                   20                  25                  30

Glu Asp Ile Ser Gln Val Leu His Val Ser Gln Gln Ile Xaa  
           35                  40                  45

&lt;210&gt; 183

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (41)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 183

Met Ala Leu Gly Leu Cys Ser Ser Gly Ala Leu Ser Thr Leu Cys Leu  
   1                  5                  10                  15

Ser Ser Val Thr Cys Leu Ala Ile Met Val Leu Met Ala Val Asp Gly  
                   20                  25                  30

Leu His Gly Thr Ser Gly Leu Gly Xaa  
           35                  40

&lt;210&gt; 184

&lt;211&gt; 80

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (80)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 184

Met Thr Leu Met Cys Leu Cys Leu Ser Val Thr Val Leu His Pro Leu  
   1                  5                  10                  15

Arg Ser Lys Glu Arg Leu Ser Gly Thr Phe Cys Gly Tyr Ser Ser Ser  
           20                  25                  30

Trp Cys Ser Pro Ala Ser Glu Ser Ser Ser Pro Gly Ser Leu Leu Thr  
           35                  40                  45

Cys Ala Ala Ser Gly Ser His Pro Asp Cys Pro Leu Ser Gln Arg Leu  
           50                  55                  60

Leu Gly Val Gln Leu Ala Ala Leu Gly Arg Pro Gln Gly Leu Phe Xaa  
   65                  70                  75                  80

```

<400> 185
Met Lys Ser Gln Cys Tyr Ser Pro Ser Tyr Phe Ala Phe Phe Cys Leu
  1                      5                      10                      15
Val Phe Phe Gln Ile Thr Ser Ala Ser Ser Gln Thr Leu Arg Gly His
      20                      25                      30
Val Leu Cys Arg Thr Thr Leu Arg Asp Ser Ser Ala Tyr Cys Xaa
      35                      40                      45

```

```
<210> 186
<211> 141
<212> PRT
<213> Homo sapiens
```

```
<220>
<221> SITE
<222> (36)
<223> Xaa equals any of the naturally occurring L-amino acids
```

```
<220>
<221> SITE
<222> (141)
<223> Xaa equals stop translation
```

```

<400> 186
Met Phe Leu Phe Gly Gly Phe Leu Met Thr Leu Phe Gly Leu Phe Val
  1             5             10             15
Ser Leu Val Phe Leu Gly Gln Ala Phe Thr Ile Met Leu Val Tyr Val
      20             25             30
Trp Ser Arg Xaa Asn Pro Tyr Val Arg Met Asn Phe Phe Gly Leu Leu
      35             40             45
Asn Phe Gln Ala Pro Phe Leu Pro Trp Val Leu Met Gly Phe Ser Leu
      50             55             60
Leu Leu Gly Asn Ser Ile Ile Val Asp Leu Leu Gly Ile Ala Val Gly
      65             70             75             80

```

109

His Ile Tyr Phe Phe Leu Glu Asp Val Phe Pro Asn Gln Pro Gly Gly  
                     85                    90                    95

Ile Arg Ile Leu Lys Thr Pro Ser Ile Leu Lys Ala Ile Phe Asp Thr  
                     100                    105                    110

Pro Asp Glu Asp Pro Asn Tyr Asn Pro Leu Pro Glu Glu Arg Pro Gly  
                     115                    120                    125

Gly Phe Ala Trp Gly Glu Gly Gln Arg Leu Gly Gly Xaa  
                     130                    135                    140

<210> 187  
 <211> 339  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (339)  
 <223> Xaa equals stop translation

<400> 187  
 Met Arg Lys Pro Ala Ala Gly Phe Leu Pro Ser Leu Leu Lys Val Leu  
   1                    5                    10                    15

Leu Leu Pro Leu Ala Pro Ala Ala Ala Gln Asp Ser Thr Gln Ala Ser  
                     20                    25                    30

Thr Pro Gly Ser Pro Leu Ser Pro Thr Glu Tyr Glu Arg Phe Phe Ala  
                     35                    40                    45

Leu Leu Thr Pro Thr Trp Lys Ala Glu Thr Thr Cys Arg Leu Arg Ala  
                     50                    55                    60

Thr His Gly Cys Arg Asn Pro Thr Leu Val Gln Leu Asp Gln Tyr Glu  
   65                    70                    75                    80

Asn His Gly Leu Val Pro Asp Gly Ala Val Cys Ser Asn Leu Pro Tyr  
                     85                    90                    95

Ala Ser Trp Phe Glu Ser Phe Cys Gln Phe Thr His Tyr Arg Cys Ser  
                     100                    105                    110

Asn His Val Tyr Tyr Ala Lys Arg Val Leu Cys Ser Gln Pro Val Ser  
                     115                    120                    125

Ile Leu Ser Pro Asn Thr Leu Lys Glu Ile Glu Ala Ser Ala Glu Val  
                     130                    135                    140

Ser Pro Thr Thr Met Thr Ser Pro Ile Ser Pro His Phe Thr Val Thr  
  145                    150                    155                    160

Glu Arg Gln Thr Phe Gln Pro Trp Pro Glu Arg Leu Ser Asn Asn Val

110

	165		170		175
Glu Glu Leu Leu Gln Ser Ser Leu Ser Leu Gly Ser Gln Glu Gln Ala	180		185		190
Pro Glu His Lys Gln Glu Gln Gly Val Glu His Arg Gln Glu Pro Thr	195		200		205
Gln Glu His Lys Gln Glu Glu Gly Gln Lys Gln Glu Glu Gln Glu Glu	210		215		220
Glu Gln Glu Glu Glu Gly Lys Gln Glu Glu Gly Gln Gly Thr Lys Glu	225		230		235
Gly Arg Glu Ala Val Ser Gln Leu Gln Thr Asp Ser Glu Pro Lys Phe	245		250		255
His Ser Glu Ser Leu Ser Ser Asn Pro Ser Ser Phe Ala Pro Arg Val	260		265		270
Arg Glu Val Glu Ser Thr Pro Met Ile Met Glu Asn Ile Gln Glu Leu	275		280		285
Ile Arg Ser Ala Gln Glu Ile Asp Glu Met Asn Glu Ile Tyr Asp Glu	290		295		300
Asn Ser Tyr Trp Arg Asn Gln Asn Pro Gly Ser Leu Leu Gln Leu Pro	305		310		315
His Thr Glu Pro Cys Trp Cys Cys Ala Ile Arg Ser Trp Arg Ile Pro	325		330		335

Ala Ser Xaa

&lt;210&gt; 188

&lt;211&gt; 66

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (66)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 188

Met	Gln	Arg	Ile	Pro	Thr	Ser	Pro	Arg	Gln	Ala	Trp	Trp	Trp	Thr	Cys
1				5					10					15	

Trp	Ala	Met	Phe	Gln	Gly	Pro	Ala	Ala	Gly	Ser	Val	Gly	Ala	Glu	Arg
		20					25						30		

Lys	Gly	Glu	Gly	Cys	Leu	Phe	Phe	Gly	Gln	Asp	Glu	Ser	Ser	Arg	Cys
		35					40					45			



Gly Arg Ser Trp Pro Leu Ala Asp Pro Trp Val Tyr Arg Val Leu Arg  
 50 55 60

Ser Xaa  
 65

<210> 189  
 <211> 360  
 <212> PRT  
 <213> Homo sapiens

<400> 189  
 Met Val Pro Ala Ala Gly Arg Arg Pro Pro Arg Val Met Arg Leu Leu  
 1 5 10 15

Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu Pro Val Arg Gly  
 20 25 30

Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser Glu Glu Gln Pro  
 35 40 45

Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly Glu Glu Glu Leu  
 50 55 60

Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu Glu Ala Asn Ala  
 65 70 75 80

Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val Met Leu Ser Val  
 85 90 95

Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu Pro Ser Gly Val  
 100 105 110

Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys Asn Val Arg Glu  
 115 120 125

Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe Pro Asp Arg Glu  
 130 135 140

Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser Asp Ala Ala Pro  
 145 150 155 160

Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser Pro Lys Val Asn  
 165 170 175

Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe Thr Leu Lys Ile  
 180 185 190

Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn Pro Asn Gly Ser  
 195 200 205

Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys Arg Phe Ser Ala  
 210 215 220

Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala Phe Pro Ala Leu  
 225 230 235 240  
 His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser Leu Ser Thr Arg  
 245 250 255  
 Phe Gly Thr Val Ala Val Pro Asn Ile Leu Leu Phe Gln Gly Ala Lys  
 260 265 270  
 Pro Met Ala Arg Phe Asn His Thr Asp Arg Thr Leu Glu Thr Leu Lys  
 275 280 285  
 Ile Phe Ile Phe Asn Gln Thr Gly Ile Glu Ala Lys Lys Asn Val Val  
 290 295 300  
 Val Thr Gln Ala Asp Gln Ile Gly Pro Leu Pro Ser Thr Leu Ile Lys  
 305 310 315 320  
 Ser Val Asp Trp Leu Leu Val Phe Ser Leu Phe Phe Leu Ile Ser Phe  
 325 330 335  
 Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg Trp Leu Ile Pro  
 340 345 350  
 Gly Gln Glu Gln Glu His Val Glu  
 355 360

<210> 190  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (160)  
 <223> Xaa equals stop translation

<400> 190  
 Met Leu Leu Leu Leu Ile Phe Trp Ile Ala Pro Ala His Gly Pro Thr  
 1 5 10 15  
 Asn Ile Met Val Tyr Ile Ser Ile Cys Ser Leu Leu Gly Ser Phe Thr  
 20 25 30  
 Val Pro Ser Thr Lys Gly Ile Gly Leu Ala Ala Gln Asp Ile Leu His  
 35 40 45  
 Asn Asn Pro Ser Ser Gln Arg Ala Leu Cys Leu Cys Leu Val Leu Leu  
 50 55 60  
 Ala Val Leu Gly Cys Ser Ile Ile Val Gln Phe Arg Tyr Ile Asn Lys  
 65 70 75 80

113

Ala Leu Glu Cys Phe Asp Ser Ser Val Phe Gly Ala Ile Tyr Tyr Val  
                     85                    90                    95

Val Phe Thr Thr Leu Val Leu Leu Ala Ser Ala Ile Leu Phe Arg Glu  
                     100                    105                    110

Trp Ser Asn Val Gly Leu Val Asp Phe Leu Gly Met Ala Cys Gly Phe  
                     115                    120                    125

Thr Thr Val Ser Val Gly Ile Val Leu Ile Gln Val Phe Lys Glu Phe  
                     130                    135                    140

Asn Phe Asn Leu Gly Glu Met Asn Lys Ser Asn Met Lys Thr Asp Xaa  
                     145                    150                    155                    160

&lt;210&gt; 191

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (92)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (96)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (101)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 191

Met Phe Val Ala Val Phe Tyr Trp Val Leu Thr Val Phe Phe Leu Ile  
   1                    5                    10                    15

Ile Tyr Ile Thr Met Thr Tyr Thr Arg Ile Pro Gln Val Pro Trp Thr  
                     20                    25                    30

Thr Val Gly Leu Cys Phe Asn Gly Ser Ala Phe Val Leu Tyr Leu Ser  
                     35                    40                    45

Ala Ala Val Val Asp Ala Ser Ser Val Ser Pro Glu Lys Asp Ser His  
                     50                    55                    60

Asn Phe Asn Ser Trp Ala Ala Ser Ser Phe Phe Ala Phe Leu Val Thr  
   65                    70                    75                    80

114

Ile Cys Tyr Ala Gly Asn Thr Tyr Phe Ser Phe Xaa Ala Trp Arg Xaa  
                             85                            90                            95

Arg Thr Ile Gln Xaa  
                             100

<210> 192  
 <211> 43  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (43)  
 <223> Xaa equals stop translation

<400> 192  
 Met Phe Lys Leu Gln Leu Asp Leu Leu Thr Ala Val Asn Leu Val Tyr  
       1                            5                            10                            15

Phe Ser Phe Leu Trp Val Val Ser Val Ala Asn Lys Met Asp Val Ser  
                             20                            25                            30

Val Phe Glu Leu Val Asn Ser Asp Cys Phe Xaa  
                             35                            40

<210> 193  
 <211> 62  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (62)  
 <223> Xaa equals stop translation

<400> 193  
 Met Ser Val Cys Val Phe Leu Asp Phe Arg Leu Ile Phe Trp Ser Phe  
       1                            5                            10                            15

Cys Pro Cys Ser Ala Ser Pro Ser Arg His Phe Ala Ser Ser Ser Arg  
                             20                            25                            30

Gly Gly Gly Gly Gly Ser Arg Asn Trp Val Gly Ala Gly Ala Ser Leu  
                             35                            40                            45

Ala Ala Ser Leu Ala Leu Tyr Ala Leu Ser Pro Arg Arg Xaa  
                             50                            55                            60

<210> 194  
 <211> 53  
 <212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (53)

<223> Xaa equals stop translation

<400> 194

Met Gln Ala Gln Ile Ser Ser Pro Arg Trp Thr Ser Trp Phe Ser Leu  
1 5 10 15

Thr Ala Val Thr Leu Ala Phe Pro Ser Leu Ile Pro Tyr Pro Ser Cys  
20 25 30

Gly Ile Pro Val Leu Thr Gln Asp Ala Lys Trp Pro Ser Asp Tyr Thr  
35 40 45

Ser Pro Asp Ser Xaa  
50

<210> 195

<211> 186

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (114)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (186)

<223> Xaa equals stop translation

<400> 195

Met Thr Leu Leu Asn Leu Leu Leu Gln Thr Ile Phe Tyr Gly Val Thr  
1 5 10 15

Cys Leu Asp Asp Val Leu Lys Arg Thr Lys Gly Gly Lys Asp Ile Lys  
20 25 30

Phe Leu Thr Ala Phe Arg Asp Leu Leu Phe Thr Thr Leu Ala Phe Pro  
35 40 45

Val Ser Thr Phe Val Phe Leu Ala Phe Trp Ile Leu Phe Leu Tyr Asn  
50 55 60

Arg Asp Leu Ile Tyr Pro Lys Val Leu Asp Thr Val Ile Pro Val Trp  
65 70 75 80

Leu Asn His Ala Met His Thr Phe Ile Phe Pro Ile Thr Leu Ala Glu  
85 90 95

116

Val Val Leu Arg Pro His Ser Tyr Pro Ser Lys Lys Thr Gly Leu Thr  
                   100                  105                  110  
 Leu Xaa Ala Ala Ala Ser Ile Ala Tyr Ile Ser Arg Ile Leu Trp Leu  
                   115                  120                  125  
 Tyr Phe Glu Thr Gly Thr Trp Val Tyr Pro Val Phe Ala Lys Leu Ser  
           130                  135                  140  
 Leu Leu Gly Leu Ala Ala Phe Phe Ser Leu Ser Tyr Val Phe Ile Ala  
 145                  150                  155                  160  
 Ser Ile Tyr Leu Leu Gly Glu Lys Leu Asn His Trp Lys Trp Gly Asp  
                   165                  170                  175  
 Met Arg Gln Pro Arg Lys Lys Arg Lys Xaa  
                   180                  185

<210> 196  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (77)  
 <223> Xaa equals stop translation

<400> 196  
 Met Lys Asn Ala Thr Leu Leu Arg Met Val Leu Phe Val Ile Asn Leu  
   1                  5                  10                  15  
 Gln Asn Leu Lys Ser Cys Pro Val Leu His Ile His Gln Asp Val Gln  
                   20                  25                  30  
 Gln Gln Lys Arg Met Gly His Gly Gly Ser Ser Thr Arg Val Thr Val  
           35                  40                  45  
 Thr Ser Leu Ile Arg His Cys Thr Val Phe Gln Arg Pro Lys Asn Cys  
   50                  55                  60  
 Val Gln Asn Met Ile Thr Leu Gln Leu Ser Phe Pro Xaa  
   65                  70                  75

<210> 197  
 <211> 175  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (175)  
 <223> Xaa equals stop translation

117

&lt;400&gt; 197

Met Phe Val Pro Ser Cys Leu Cys Leu Arg Phe Val Val Thr Ser Leu  
 1 5 10 15

Leu Leu Gln Met Thr His Ser Cys Gly Gly Phe Tyr Ile Cys Val Ile  
 20 25 30

Phe Glu Thr Ile Leu Ser Glu Phe Lys Thr Gln Ile Gly Arg Leu Tyr  
 35 40 45

Arg Lys Arg His Ile Gln Arg Lys Glu Ser Pro Lys Gly Arg Phe Val  
 50 55 60

Met Leu Leu Pro Ser Ser Thr His Thr Ile Pro Phe Tyr Pro Asn Pro  
 65 70 75 80

Leu His Pro Arg Pro Phe Pro Ser Ser Arg Leu Pro Pro Gly Ile Ile  
 85 90 95

Gly Gly Glu Tyr Asp Gln Arg Pro Thr Leu Pro Tyr Val Gly Asp Pro  
 100 105 110

Ile Ser Ser Leu Ile Pro Gly Pro Gly Glu Thr Pro Ser Gln Phe Pro  
 115 120 125

Pro Leu Arg Pro Arg Phe Asp Pro Val Gly Pro Leu Pro Gly Pro Asn  
 130 135 140

Pro Ile Leu Pro Gly Arg Gly Gly Pro Asn Asp Arg Phe Pro Phe Arg  
 145 150 155 160

Pro Ser Arg Gly Arg Pro Thr Asp Gly Arg Leu Ser Phe Met Xaa  
 165 170 175

&lt;210&gt; 198

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (51)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 198

Met Gly Leu Lys Arg Lys Gln Gly Phe Val Phe Leu Phe Leu Leu Leu  
 1 5 10 15

Lys Ser Thr Val Ala Ser Trp Leu Leu Ser Gly Val Gly Arg Ile Trp  
 20 25 30

Gly Leu Val His Phe Val Lys Val Asn His Val Cys Leu Asn Asn Arg  
 35 40 45

Gly Val Xaa  
50

```
<210> 199
<211> 190
<212> PRT
<213> Homo sapiens
```

```
<220>  
<221> SITE  
<222> (190)  
<223> Xaa equals stop translation
```

<400> 199																
Met	Gly	Pro	Val	Arg	Leu	Gly	Ile	Leu	Leu	Phe	Leu	Phe	Leu	Ala	Val	
1				5					10					15		
His	Glu	Ala	Trp	Ala	Gly	Met	Leu	Lys	Glu	Glu	Asp	Asp	Asp	Thr	Glu	
			20					25					30			
Arg	Leu	Pro	Ser	Lys	Cys	Glu	Val	Cys	Lys	Leu	Leu	Ser	Thr	Glu	Leu	
		35					40					45				
Gln	Ala	Glu	Leu	Ser	Arg	Thr	Gly	Arg	Ser	Arg	Glu	Val	Leu	Glu	Leu	
	50					55					60					
Gly	Gln	Val	Leu	Asp	Thr	Gly	Lys	Arg	Lys	Arg	His	Val	Pro	Tyr	Ser	
65					70					75					80	
Val	Ser	Glu	Thr	Arg	Leu	Glu	Glu	Ala	Leu	Glu	Asn	Leu	Cys	Glu	Arg	
				85					90					95		
Ile	Leu	Asp	Tyr	Ser	Val	His	Ala	Glu	Arg	Lys	Gly	Ser	Leu	Arg	Tyr	
			100					105					110			
Ala	Lys	Gly	Gln	Ser	Gln	Thr	Met	Ala	Thr	Leu	Lys	Gly	Leu	Val	Gln	
		115				120						125				
Lys	Gly	Val	Lys	Val	Asp	Leu	Gly	Ile	Pro	Leu	Glu	Leu	Trp	Asp	Glu	
	130					135					140					
Pro	Ser	Val	Glu	Val	Thr	Tyr	Leu	Lys	Lys	Gln	Cys	Glu	Thr	Met	Leu	
145					150					155					160	
Glu	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Glu	Gly	Gly	Asp	Lys	Met	Thr	
				165				170						175		
Lys	Thr	Gly	Ser	His	Pro	Lys	Leu	Asp	Arg	Glu	Asp	Leu	Xaa			
			180					185					190			

```
<210> 200
<211> 80
```



&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (80)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 200

```

Met Asn Tyr Ser Arg Ser Pro Trp Ala Ala Val Met Glu Pro Leu Thr
  1              5              10              15

Leu Leu Phe Leu His Leu Ser Cys Leu Leu Ser Leu Cys Glu Ala Val
              20              25              30

Gly Trp Asp Ser Glu Cys Leu Val Cys Ser Leu Gly Glu Glu Glu Phe
              35              40              45

Leu Arg Met Gln Ala Leu Leu Cys Gly Cys Arg Leu His Leu Gly Gly
              50              55              60

Val Leu Tyr Val Cys Thr Leu Gly Thr Ala Cys Ile Trp Lys Ile Xaa
  65              70              75              80

```

&lt;210&gt; 201

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (106)

&lt;223&gt; Xaa equals stop translation

&lt;400&gt; 201

```

Met Asn Leu Gly Val Ser Met Leu Arg Ile Leu Phe Leu Leu Asp Val
  1              5              10              15

Gly Gly Ala Gln Val Leu Ala Thr Gly Lys Thr Pro Gly Ala Glu Ile
              20              25              30

Asp Phe Lys Tyr Ala Leu Ile Gly Thr Ala Val Gly Val Ala Ile Ser
              35              40              45

Ala Gly Phe Leu Ala Leu Lys Ile Cys Met Ile Arg Arg His Leu Phe
              50              55              60

Asp Asp Asp Ser Ser Asp Leu Lys Ser Thr Pro Gly Gly Leu Ser Asp
  65              70              75              80

Thr Ile Pro Leu Lys Lys Arg Ala Pro Arg Arg Asn His Asn Phe Ser

```

120

85 90 95  
 Lys Arg Asp Ala Gln Val Ile Glu Leu Xaa  
 100 105  
  
 <210> 202  
 <211> 80  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (80)  
 <223> Xaa equals stop translation  
  
 <400> 202  
 Met Ala Cys Leu Gly Gly Leu Leu Gly Ile Ile Gly Val Ile Cys Leu  
 1 5 10 15  
 Ile Ser Cys Leu Ser Pro Glu Met Asn Cys Asp Gly Gly His Ser Tyr  
 20 25 30  
 Val Arg Asn Tyr Leu Gln Lys Pro Thr Phe Ala Leu Gly Glu Leu Tyr  
 35 40 45  
 Pro Pro Leu Ile Asn Leu Trp Glu Ala Gly Lys Glu Lys Ser Thr Ser  
 50 55 60  
 Leu Lys Val Lys Ala Thr Val Ile Gly Leu Pro Thr Asn Met Ser Xaa  
 65 70 75 80

<210> 203  
 <211> 58  
 <212> PRT  
 <213> Homo sapiens  
  
 <220>  
 <221> SITE  
 <222> (58)  
 <223> Xaa equals stop translation  
  
 <400> 203  
 Met Gly Leu Lys Leu Leu Gln Lys Pro Gly Ser Leu Lys Thr Leu Ile  
 1 5 10 15  
 Ala Ile Ile Leu Val Met Tyr Ile Phe Met Thr Ile Ser Val Ile Ala  
 20 25 30  
 Gly Thr Gly Lys Phe Ser Gln Lys Leu Asp Leu His Leu Asn Met Asp  
 35 40 45

Ile Ser Pro Gly Arg Pro Ser Val His Xaa  
 50 55

<210> 204

<211> 161

<212> PRT

<213> Homo sapiens

<400> 204

Met Asp Phe Leu Asn Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe  
 1 5 10 15

Tyr Thr Pro Trp Cys Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn  
 20 25 30

Ser Leu Pro Arg Ala Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala  
 35 40 45

Ser Gln His Ser Ser Leu Ser Thr Arg Phe Gly Thr Val Ala Val Pro  
 50 55 60

Asn Ile Leu Leu Phe Gln Gly Ala Lys Pro Met Ala Arg Phe Asn His  
 65 70 75 80

Thr Asp Arg Thr Leu Glu Thr Leu Lys Ile Phe Ile Phe Asn Gln Thr  
 85 90 95

Gly Ile Glu Ala Lys Lys Asn Val Val Val Thr Gln Ala Asp Gln Ile  
 100 105 110

Gly Pro Leu Pro Ser Thr Leu Ile Lys Ser Val Asp Trp Leu Leu Val  
 115 120 125

Phe Ser Leu Phe Phe Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg  
 130 135 140

Thr Glu Ser Ile Arg Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val  
 145 150 155 160

Glu

<210> 205

<211> 137

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

122

&lt;400&gt; 205

Ile Pro Glu Asn Arg Arg Pro Ala Ser Xaa Cys Thr Trp Ser Met Trp  
 1 5 10 15

Thr Ser Arg Thr Thr Thr Arg Arg Pro Pro Trp Gly Arg Phe Ser Ser  
 20 25 30

Val Ser Ser Ala Ser Val Ser Ser Thr Arg Lys Thr Trp Arg Thr Arg  
 35 40 45

Ser Thr Ser Cys Cys Arg Ser Ser Arg Arg Arg Val Ala Ala Pro Phe  
 50 55 60

Cys Thr Pro Ser Ala Ser Thr Glu Pro Ser Ala Arg Met Glu Pro Pro  
 65 70 75 80

Leu Glu Leu Pro Val Val His Thr Phe Ser Phe Leu Thr Phe Val Phe  
 85 90 95

Thr Tyr Arg Cys Ser Ala Gly Asp Gly Ser Ile Thr Gln Ile Asn Cys  
 100 105 110

Ala Tyr Glu Met Gly Glu Glu Met Pro Lys Arg Gln Met Lys Ala Ile  
 115 120 125

Lys Phe Leu Leu Phe His Phe Tyr Leu  
 130 135

&lt;210&gt; 206

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (10)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 206

Ile Pro Glu Asn Arg Arg Pro Ala Ser Xaa Cys Thr Trp Ser Met Trp  
 1 5 10 15

Thr Ser Arg Thr Thr Thr Arg Arg Pro Pro Trp Gly Arg Phe Ser Ser  
 20 25 30

Val Ser Ser Ala Ser Val Ser Ser Thr  
 35 40

&lt;210&gt; 207

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

123

&lt;400&gt; 207

Arg Lys Thr Trp Arg Thr Arg Ser Thr Ser Cys Cys Arg Ser Ser Arg  
 1 5 10 15

Arg Arg Val Ala Ala Pro Phe Cys Thr Pro Ser Ala Ser Thr Glu Pro  
 20 25 30

Ser Ala Arg Met Glu Pro Pro Leu Glu Leu Pro  
 35 40

&lt;210&gt; 208

&lt;211&gt; 53

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 208

Val Val His Thr Phe Ser Phe Leu Thr Phe Val Phe Thr Tyr Arg Cys  
 1 5 10 15

Ser Ala Gly Asp Gly Ser Ile Thr Gln Ile Asn Cys Ala Tyr Glu Met  
 20 25 30

Gly Glu Glu Met Pro Lys Arg Gln Met Lys Ala Ile Lys Phe Leu Leu  
 35 40 45

Phe His Phe Tyr Leu  
 50

&lt;210&gt; 209

&lt;211&gt; 223

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 209

His Pro Ser Ile Ile Ile Trp Ser Gly Asn Asn Glu Asn Glu Glu Ala  
 1 5 10 15

Leu Met Met Asn Trp Tyr His Ile Ser Phe Thr Asp Arg Pro Ile Tyr  
 20 25 30

Ile Lys Asp Tyr Val Thr Leu Tyr Val Lys Asn Ile Arg Glu Leu Val  
 35 40 45

Leu Ala Gly Asp Lys Ser Arg Pro Phe Ile Thr Ser Ser Pro Thr Asn  
 50 55 60

Gly Ala Glu Thr Val Ala Glu Ala Trp Val Ser Gln Asn Pro Asn Ser  
 65 70 75 80

Asn Tyr Phe Gly Asp Val His Phe Tyr Asp Tyr Ile Ser Asp Cys Trp  
 85 90 95

Asn Trp Lys Val Phe Pro Lys Ala Arg Phe Ala Ser Glu Tyr Gly Tyr

124

100	105	110
Gln Ser Trp Pro Ser Phe Ser Thr Leu Glu Lys Val Ser Ser Thr Glu		
115	120	125
Asp Trp Ser Phe Asn Ser Lys Phe Ser Leu His Arg Gln His His Glu		
130	135	140
Gly Gly Asn Lys Gln Met Leu Tyr Gln Ala Gly Leu His Phe Lys Leu		
145	150	155
Pro Gln Ser Thr Asp Pro Leu Arg Thr Phe Lys Asp Thr Ile Tyr Leu		
	165	170
Thr Gln Val Met Gln Ala Gln Cys Val Lys Thr Glu Thr Glu Phe Tyr		
	180	185
Arg Arg Ser Arg Ser Glu Ile Val Asp Gln Gln Gly His Thr Met Gly		
	195	200
Ala Leu Tyr Trp Gln Leu Asn Asp Ile Trp Gln Ala Pro Ser Trp		
210	215	220
<210> 210		
<211> 160		
<212> PRT		
<213> Homo sapiens		
<400> 210		
Val Arg Val His Thr Trp Ser Ser Leu Glu Pro Val Cys Ser Arg Val		
1	5	10
Thr Glu Arg Phe Val Met Lys Gly Gly Glu Ala Val Cys Leu Tyr Glu		
	20	25
Glu Pro Val Ser Glu Leu Leu Arg Arg Cys Gly Asn Cys Thr Arg Glu		
	35	40
Ser Cys Val Val Ser Phe Tyr Leu Ser Ala Asp His Glu Leu Leu Ser		
	50	55
Pro Thr Asn Tyr His Phe Leu Ser Ser Pro Lys Glu Ala Val Gly Leu		
	65	70
Cys Lys Ala Gln Ile Thr Ala Ile Ile Ser Gln Gln Gly Asp Ile Phe		
	85	90
Val Phe Asp Leu Glu Thr Ser Ala Val Ala Pro Phe Val Trp Leu Asp		
	100	105
Val Gly Ser Ile Pro Gly Arg Phe Ser Asp Asn Gly Phe Leu Met Thr		
	115	120
Glu Lys Thr Arg Thr Ile Leu Phe Tyr Pro Trp Glu Pro Thr Ser Lys		

125

130

135

140

Asn Glu Leu Glu Gln Ser Phe His Val Thr Ser Leu Thr Asp Ile Tyr  
 145 150 155 160

&lt;210&gt; 211

&lt;211&gt; 171

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (102)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 211

Pro Arg Leu Thr Pro Arg Met Lys Trp Pro Thr Ala Ala Leu Ala Ser  
 1 5 10 15

Arg Leu Leu Gly Trp Thr Val Leu Arg Pro Pro Tyr Pro Arg Val Pro  
 20 25 30

Ser Leu Pro Gln Val Thr Leu His Pro Thr Asp Gly Leu Met Ala Val  
 35 40 45

Leu Tyr Thr Gly Gly Glu Gly Arg Thr Leu Gly Glu Gln His Phe Phe  
 50 55 60

His Glu Thr Phe Val Thr Arg Trp Leu Leu Gly Pro Val Pro Val Arg  
 65 70 75 80

Phe Gly Ala Cys Ser Pro Leu Ser Phe Leu Ala Pro Arg Arg Gly Gln  
 85 90 95

Gly Ala Pro Ala Gly Xaa Phe Cys Ala Cys Pro Arg Pro Ala Ser Arg  
 100 105 110

Gln Leu Cys Pro Trp Pro Ala Leu Pro Gly Thr Pro Tyr Ser Asn Ser  
 115 120 125

Ala Pro Leu Cys Thr Gly Met Gly His Ser Asn Thr Pro Gln Gly Pro  
 130 135 140

Pro Ser Pro Gln Tyr Ala Leu Ser Pro Thr Glu Pro Thr Ser Leu Ser  
 145 150 155 160

Gly Asn Ser His Leu Pro Ala Ile Leu Val Leu  
 165 170

&lt;210&gt; 212

126

<211> 41  
 <212> PRT  
 <213> Homo sapiens

<400> 212  
 Pro Arg Leu Thr Pro Arg Met Lys Trp Pro Thr Ala Ala Leu Ala Ser  
     1                    5                    10                    15  
 Arg Leu Leu Gly Trp Thr Val Leu Arg Pro Pro Tyr Pro Arg Val Pro  
                     20                    25                    30  
 Ser Leu Pro Gln Val Thr Leu His Pro  
                     35                    40

<210> 213  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

<400> 213  
 Thr Asp Gly Leu Met Ala Val Leu Tyr Thr Gly Gly Glu Gly Arg Thr  
     1                    5                    10                    15  
 Leu Gly Glu Gln His Phe Phe His Glu Thr Phe Val Thr Arg Trp Leu  
                     20                    25                    30  
 Leu Gly Pro Val Pro Val Arg Phe Gly  
                     35                    40

<210> 214  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (20)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 214  
 Ala Cys Ser Pro Leu Ser Phe Leu Ala Pro Arg Arg Gly Gln Gly Ala  
     1                    5                    10                    15  
 Pro Ala Gly Xaa Phe Cys Ala Cys Pro Arg Pro Ala Ser Arg Gln Leu  
                     20                    25                    30  
 Cys Pro Trp Pro Ala Leu Pro Gly Thr Pro  
                     35                    40

<210> 215  
 <211> 47  
 <212> PRT



127

&lt;213&gt; Homo sapiens

&lt;400&gt; 215

Tyr Ser Asn Ser Ala Pro Leu Cys Thr Gly Met Gly His Ser Asn Thr  
 1 5 10 15  
 Pro Gln Gly Pro Pro Ser Pro Gln Tyr Ala Leu Ser Pro Thr Glu Pro  
 20 25 30  
 Thr Ser Leu Ser Gly Asn Ser His Leu Pro Ala Ile Leu Val Leu  
 35 40 45

&lt;210&gt; 216

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 216

His Leu Leu Glu Val Thr Pro Cys Arg Leu Pro Val Pro Glu Phe Pro  
 1 5 10 15  
 Gly Arg Thr Pro Arg Gly Ser Arg Thr Pro Asp  
 20 25

&lt;210&gt; 217

&lt;211&gt; 239

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 217

Met Ile Pro Gly Ser Asp Ser Gln Thr Ala Leu Asn Phe Gly Ser Thr  
 1 5 10 15  
 Leu Met Lys Lys Lys Ser Asp Pro Glu Gly Pro Ala Leu Leu Phe Pro  
 20 25 30  
 Glu Ser Glu Leu Ser Ile Arg Ile Gly Arg Ala Gly Leu Leu Ser Asp  
 35 40 45  
 Lys Ser Glu Asn Gly Glu Ala Tyr Gln Arg Lys Lys Ala Ala Ala Thr  
 50 55 60  
 Gly Leu Pro Glu Gly Pro Ala Val Pro Val Pro Ser Arg Gly Asn Leu  
 65 70 75 80  
 Ala Gln Pro Gly Gly Ser Ser Trp Arg Arg Ile Ala Leu Leu Ile Leu  
 85 90 95  
 Ala Ile Thr Ile His Asn Val Pro Glu Gly Leu Ala Val Gly Val Gly  
 100 105 110  
 Phe Gly Ala Ile Glu Lys Thr Ala Ser Ala Thr Phe Glu Ser Ala Arg  
 115 120 125

Asn Leu Ala Ile Gly Ile Gly Ile Gln Asn Phe Pro Glu Gly Leu Ala  
 130 135 140

Val Ser Leu Pro Leu Arg Gly Ala Gly Phe Ser Thr Trp Arg Ala Phe  
 145 150 155 160

Trp Tyr Gly Gln Leu Ser Gly Met Val Glu Pro Leu Ala Gly Val Phe  
 165 170 175

Gly Ala Phe Ala Val Val Leu Ala Glu Pro Ile Leu Pro Tyr Ala Leu  
 180 185 190

Ala Phe Ala Ala Gly Ala Met Val Tyr Val Val Met Asp Asp Ile Ile  
 195 200 205

Pro Glu Ala Gln Ile Ser Gly Asn Gly Lys Leu Ala Ser Trp Ala Ser  
 210 215 220

Ile Leu Gly Phe Val Val Met Met Ser Leu Asp Val Gly Leu Gly  
 225 230 235

<210> 218

<211> 43

<212> PRT

<213> Homo sapiens

<400> 218

Met Ile Pro Gly Ser Asp Ser Gln Thr Ala Leu Asn Phe Gly Ser Thr  
 1 5 10 15

Leu Met Lys Lys Lys Ser Asp Pro Glu Gly Pro Ala Leu Leu Phe Pro  
 20 25 30

Glu Ser Glu Leu Ser Ile Arg Ile Gly Arg Ala  
 35 40

<210> 219

<211> 41

<212> PRT

<213> Homo sapiens

<400> 219

Gly Leu Leu Ser Asp Lys Ser Glu Asn Gly Glu Ala Tyr Gln Arg Lys  
 1 5 10 15

Lys Ala Ala Ala Thr Gly Leu Pro Glu Gly Pro Ala Val Pro Val Pro  
 20 25 30

Ser Arg Gly Asn Leu Ala Gln Pro Gly  
 35 40

129

&lt;210&gt; 220

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 220

Gly Ser Ser Trp Arg Arg Ile Ala Leu Leu Ile Leu Ala Ile Thr Ile  
 1 5 10 15

His Asn Val Pro Glu Gly Leu Ala Val Gly Val Gly Phe Gly Ala Ile  
 20 25 30

Glu Lys Thr Ala Ser Ala Thr Phe Glu Ser Ala Arg  
 35 40

&lt;210&gt; 221

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 221

Asn Leu Ala Ile Gly Ile Gly Ile Gln Asn Phe Pro Glu Gly Leu Ala  
 1 5 10 15

Val Ser Leu Pro Leu Arg Gly Ala Gly Phe Ser Thr Trp Arg Ala Phe  
 20 25 30

Trp Tyr Gly Gln Leu Ser Gly Met Val Glu Pro  
 35 40

&lt;210&gt; 222

&lt;211&gt; 43

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 222

Leu Ala Gly Val Phe Gly Ala Phe Ala Val Val Leu Ala Glu Pro Ile  
 1 5 10 15

Leu Pro Tyr Ala Leu Ala Phe Ala Ala Gly Ala Met Val Tyr Val Val  
 20 25 30

Met Asp Asp Ile Ile Pro Glu Ala Gln Ile Ser  
 35 40

&lt;210&gt; 223

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 223

Gly Asn Gly Lys Leu Ala Ser Trp Ala Ser Ile Leu Gly Phe Val Val

**1**                      **5**                      **10**                      **15**

```
<210> 224
<211> 11
<212> PRT
<213> Homo sapiens
```

<400> 224  
Thr Arg Pro Ile Thr Tyr Val Leu Leu Ala Gly  
          1               5                  10

```
<210> 225
<211> 35
<212> PRT
<213> Homo sapiens
```

<400> 225  
Gly Thr Ser Leu Thr Ala Pro Leu Leu Glu Phe Leu Leu Ala Leu Tyr  
1 5 10 15

Phe Leu Phe Ala Asp Ala Met Gln Leu Asn Asp Lys Trp Gln Gly Leu  
20 25 30

Cys Trp Pro  
35

```
<210> 226
<211> 30
<212> PRT
<213> Homo sapiens
```

<400> 226  
Leu Ala Asn Phe Glx Cys Ser Asp Cys Ala Gln Thr Val Leu Phe Val  
1 5 10 15

Leu Glx Phe Glx Ile Leu Val Phe Thr Tyr Glu Ile Pro Phe  
20 25 30

```
<210> 227
<211> 75
<212> PRT
<213> Homo sapiens
```

<400> 227  
Gln Ala Trp His Glu Val Gly Gly Gly Val Arg Arg Cys Trp Phe Val  
1 5 10 15

Leu Gly Glu Arg Arg Ala Gly Ser Leu Leu Ser Ala Ser Tyr Gly Thr

131

	20		25		30
Phe	Ala	Met	Pro	Gly	Met
	35			40	
Val	Leu	Phe	Gly	Arg	Arg
				45	
Trp	Ala	Ile	Ala		
Ser	Asp	Asp	Leu	Val	Phe
	50			55	
Pro	Gly	Phe	Phe	Glu	Leu
				60	
Val	Val	Arg	Val		
Leu	Trp	Trp	Ile	Gly	Ile
	65			70	
Leu	Thr	Leu	Tyr	Leu	
			75		

&lt;210&gt; 228

&lt;211&gt; 125

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 228

Pro	Gly	Met	Val	Leu	Phe	Gly	Arg	Arg	Trp	Ala	Ile	Ala	Ser	Asp	Asp
1				5					10					15	
Leu	Val	Phe	Pro	Gly	Phe	Phe	Glu	Leu	Val	Val	Arg	Val	Leu	Trp	Trp
			20					25					30		
Ile	Gly	Ile	Leu	Thr	Leu	Tyr	Leu	Met	His	Arg	Gly	Lys	Leu	Asp	Cys
	35						40					45			
Ala	Gly	Gly	Ala	Leu	Leu	Ser	Ser	Tyr	Leu	Ile	Val	Leu	Met	Ile	Leu
	50					55					60				
Leu	Ala	Val	Val	Ile	Cys	Thr	Val	Ser	Ala	Ile	Met	Cys	Val	Ser	Met
	65				70					75				80	
Arg	Gly	Thr	Ile	Cys	Asn	Pro	Gly	Pro	Arg	Lys	Ser	Met	Ser	Lys	Leu
				85					90					95	
Leu	Tyr	Ile	Arg	Leu	Ala	Leu	Phe	Phe	Pro	Glu	Met	Val	Trp	Ala	Ser
	100						105						110		
Leu	Gly	Ala	Ala	Trp	Val	Ala	Asp	Gly	Val	Gln	Cys	Asp			
	115						120					125			

&lt;210&gt; 229

&lt;211&gt; 18

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 229

His	Glu	Arg	Asn	Cys	Phe	Pro	Met	Trp	Leu	Asn	His	Ser	Ala	Phe	Pro
1				5					10					15	

Pro Val

132

&lt;210&gt; 230

&lt;211&gt; 132

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 230

Gly Trp Thr Arg Glu Asn Asp His Arg Ala Leu Ser Lys Ala Gly Ile  
1 5 10 15

Gly Ser Ala Glu Ile Gln Pro Ser Asn Leu Arg Val Gly Ser Ala Lys  
20 25 30

Asp Leu Gly Lys Pro Trp Ala Gly Lys Leu Leu Leu Leu Ser Ser Cys  
35 40 45

Leu Leu Phe Phe Ser Leu Gly Val Leu Tyr Arg Gly Gln Met Leu Ala  
50 55 60

Pro Pro Leu Gln Glu Asp Trp Lys Gly Gly Val Lys Asp Ser Asp Leu  
65 70 75 80

Ile Asp Asp Ser Ser Ala Ser Pro Ile Pro Pro Ser Tyr Leu Glu Tyr  
85 90 95

Lys Ala Ala Leu Tyr Pro Phe Ser Glu His Lys Ser Val Arg Asn Ala  
100 105 110

Thr Asp Ser Leu Thr Phe Phe Leu Val Thr Asp His Phe Leu Asp Asn  
115 120 125

Gln Asp Ser Gln  
130

&lt;210&gt; 231

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 231

Gly Trp Thr Arg Glu Asn Asp His Arg Ala Leu Ser Lys Ala Gly Ile  
1 5 10 15

Gly Ser Ala Glu Ile Gln Pro Ser Asn Leu Arg Val Gly Ser Ala Lys  
20 25 30

Asp Leu Gly Lys Pro Trp Ala Gly Lys Leu Leu Leu Leu  
35 40 45

&lt;210&gt; 232

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

133

&lt;400&gt; 232

Ser Ser Cys Leu Leu Phe Phe Ser Leu Gly Val Leu Tyr Arg Gly Gln  
1 5 10 15

Met Leu Ala Pro Pro Leu Gln Glu Asp Trp Lys Gly Gly Val Lys Asp  
20 25 30

Ser Asp Leu Ile Asp Asp Ser Ser Ala Ser Pro Ile Pro Pro  
35 40 45

&lt;210&gt; 233

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 233

Ser Tyr Leu Glu Tyr Lys Ala Ala Leu Tyr Pro Phe Ser Glu His Lys  
1 5 10 15

Ser Val Arg Asn Ala Thr Asp Ser Leu Thr Phe Phe Leu Val Thr Asp  
20 25 30

His Phe Leu Asp Asn Gln Asp Ser Gln  
35 40

&lt;210&gt; 234

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 234

Leu Lys Phe His Gln Glu Ser Leu Ser Gly Asp  
1 5 10

&lt;210&gt; 235

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 235

Glu Ala Lys Ser Arg Pro Val Thr Gln Ala Gly Val Gln Trp His Asp  
1 5 10 15

Leu Gly Ser Leu Gln Pro Leu Pro Pro  
20 25

&lt;210&gt; 236

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

134

&lt;400&gt; 236

Glu Ala Lys Ser Arg Pro Val Thr Gln Ala Gly Val Gln Trp His Asp  
 1 5 10 15

Leu Gly Ser Leu Gln Pro Leu Pro Pro  
 20 25

&lt;210&gt; 237

&lt;211&gt; 137

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 237

Ala Leu Val Leu Val Cys Arg Gln Arg Tyr Cys Arg Pro Arg Asp Leu  
 1 5 10 15

Leu Gln Arg Tyr Asp Ser Lys Pro Ile Val Asp Leu Ile Gly Ala Met  
 20 25 30

Glu Thr Gln Ser Glu Pro Ser Glu Leu Glu Leu Asp Asp Val Val Ile  
 35 40 45

Thr Asn Pro His Ile Glu Ala Ile Leu Glu Asn Glu Asp Trp Ile Glu  
 50 55 60

Asp Ala Ser Gly Leu Met Ser His Cys Ile Ala Ile Leu Lys Ile Cys  
 65 70 75 80

His Thr Leu Thr Glu Lys Leu Val Ala Met Thr Met Gly Ser Gly Ala  
 85 90 95

Lys Met Lys Thr Ser Ala Ser Val Ser Asp Ile Ile Val Val Ala Lys  
 100 105 110

Arg Ile Ser Pro Arg Val Asp Asp Val Val Lys Ser Met Tyr Pro Pro  
 115 120 125

Leu Asp Pro Lys Leu Leu Asp Ala Arg  
 130 135

&lt;210&gt; 238

&lt;211&gt; 319

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 238

Asp Val Glu Ser Arg Gly Pro Ser Ala Arg Cys Leu Pro Val Val Pro  
 1 5 10 15

Gly Ser Leu Leu Pro Gly Leu Glu Pro Ala Thr Lys Leu Met Pro Gly  
 20 25 30



Gly Leu Ala Pro Gly His Gly Ala Pro Val Arg Glu Leu Leu Leu Pro  
           35                                  40                                  45

Leu Leu Ser Gln Pro Thr Leu Gly Ser Leu Trp Asp Ser Leu Arg His  
           50                                  55                                  60

Cys Ser Leu Leu Cys Asn Pro Leu Ser Cys Val Pro Ala Leu Glu Ala  
           65                                  70                                  75                                  80

Pro Pro Ser Leu Val Ser Leu Gly Cys Ser Gly Gly Cys Pro Arg Leu  
                                   85                                  90                                  95

Ser Leu Ala Gly Ser Ala Ser Pro Phe Pro Phe Leu Thr Ala Leu Leu  
                                   100                                  105                                  110

Ser Leu Leu Asn Thr Leu Ala Gln Ile His Lys Gly Leu Cys Gly Gln  
           115                                  120                                  125

Leu Ala Ala Ile Leu Ala Ala Pro Gly Leu Gln Asn Tyr Phe Leu Gln  
           130                                  135                                  140

Cys Val Ala Pro Gly Ala Ala Pro His Leu Thr Pro Phe Ser Ala Trp  
           145                                  150                                  155                                  160

Ala Leu Arg His Glu Tyr His Leu Gln Tyr Leu Ala Leu Ala Leu Ala  
                                   165                                  170                                  175

Gln Lys Ala Ala Ala Leu Gln Pro Leu Pro Ala Thr His Ala Ala Leu  
                                   180                                  185                                  190

Tyr His Gly Met Ala Leu Ala Leu Leu Ser Arg Leu Leu Pro Gly Ser  
           195                                  200                                  205

Glu Tyr Leu Thr His Glu Leu Leu Leu Ser Cys Val Phe Arg Leu Glu  
           210                                  215                                  220

Phe Leu Pro Glu Arg Thr Ser Gly Gly Pro Glu Ala Ala Asp Phe Ser  
           225                                  230                                  235                                  240

Asp Gln Leu Ser Leu Gly Ser Ser Arg Val Pro Arg Cys Gly Gln Gly  
                                   245                                  250                                  255

Thr Leu Leu Ala Gln Ala Cys Gln Asp Leu Pro Ser Ile Arg Asn Cys  
                                   260                                  265                                  270

Tyr Leu Thr His Cys Ser Pro Ala Arg Ala Ser Leu Leu Ala Ser Gln  
           275                                  280                                  285

Ala Leu His Arg Gly Glu Leu Gln Arg Val Pro Thr Leu Leu Leu Pro  
           290                                  295                                  300

Met Pro Thr Glu Pro Leu Leu Pro Thr Asp Trp Pro Phe Leu His  
           305                                  310                                  315

&lt;210&gt; 239

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 239

Asp Val Glu Ser Arg Gly Pro Ser Ala Arg Cys Leu Pro Val Val Pro  
1 5 10 15

Gly Ser Leu Leu Pro Gly Leu Glu Pro Ala Thr Lys Leu Met Pro Gly  
20 25 30

Gly Leu Ala Pro Gly His Gly Ala Pro Val Arg Glu  
35 40

&lt;210&gt; 240

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 240

Leu Leu Leu Pro Leu Leu Ser Gln Pro Thr Leu Gly Ser Leu Trp Asp  
1 5 10 15

Ser Leu Arg His Cys Ser Leu Leu Cys Asn Pro Leu Ser Cys Val Pro  
20 25 30

Ala Leu Glu Ala Pro Pro Ser Leu Val Ser Leu Gly Cys  
35 40 45

&lt;210&gt; 241

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 241

Ser Gly Gly Cys Pro Arg Leu Ser Leu Ala Gly Ser Ala Ser Pro Phe  
1 5 10 15

Pro Phe Leu Thr Ala Leu Leu Ser Leu Leu Asn Thr Leu Ala Gln Ile  
20 25 30

His Lys Gly Leu Cys Gly Gln Leu Ala Ala Ile Leu Ala  
35 40 45

&lt;210&gt; 242

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 242

Ala Pro Gly Leu Gln Asn Tyr Phe Leu Gln Cys Val Ala Pro Gly Ala

137

1                      5                      10                      15  
 Ala Pro His Leu Thr Pro Phe Ser Ala Trp Ala Leu Arg His Glu Tyr  
                     20                      25                      30

His Leu Gln Tyr Leu Ala Leu Ala Leu Ala Gln Lys  
                     35                      40

<210> 243  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<400> 243  
 Ala Ala Ala Leu Gln Pro Leu Pro Ala Thr His Ala Ala Leu Tyr His  
                     1                      5                      10                      15

Gly Met Ala Leu Ala Leu Leu Ser Arg Leu Leu Pro Gly Ser Glu Tyr  
                     20                      25                      30

Leu Thr His Glu Leu Leu Leu Ser Cys Val Phe Arg  
                     35                      40

<210> 244  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<400> 244  
 Leu Glu Phe Leu Pro Glu Arg Thr Ser Gly Gly Pro Glu Ala Ala Asp  
                     1                      5                      10                      15

Phe Ser Asp Gln Leu Ser Leu Gly Ser Ser Arg Val Pro Arg Cys Gly  
                     20                      25                      30

Gln Gly Thr Leu Leu Ala Gln Ala Cys Gln Asp Leu  
                     35                      40

<210> 245  
 <211> 53  
 <212> PRT  
 <213> Homo sapiens

<400> 245  
 Pro Ser Ile Arg Asn Cys Tyr Leu Thr His Cys Ser Pro Ala Arg Ala  
                     1                      5                      10                      15

Ser Leu Leu Ala Ser Gln Ala Leu His Arg Gly Glu Leu Gln Arg Val  
                     20                      25                      30

Pro Thr Leu Leu Leu Pro Met Pro Thr Glu Pro Leu Leu Pro Thr Asp  
                     35                      40                      45

Trp Pro Phe Leu His  
50

<210> 246

<211> 25

<212> PRT

<213> Homo sapiens

<400> 246

Val Gly Ser Val Leu Gly Ala Phe Leu Thr Phe Pro Gly Leu Arg Leu  
1 5 10 15

Ala Gln Thr His Arg Asp Ala Leu Thr  
20 25

<210> 247

<211> 65

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (21)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (48)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (57)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 247

Leu Glu Cys Thr Asp Thr Ile Met Val His Cys Ser Leu Lys Leu Leu  
1 5 10 15

Ser Pro Ser Asp Xaa Ser His Ser Ala Ser Gln Val Ala Lys Thr Arg  
20 25 30

Gly Val His Xaa Thr Gln Leu Ile Phe Lys Val Phe Phe Val Xaa  
35 40 45

Met Gly Ser His Ser Thr Lys Tyr Xaa Ser Ile Arg Pro Gly Leu Leu  
50 55 60

Pro  
65

<210> 248  
<211> 14  
<212> PRT  
<213> Homo sapiens

<400> 248  
Glu Ser Ser Phe Val Pro Pro Ala Ala His Ser Ser Leu Cys  
1 5 10

<210> 249  
<211> 172  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (72)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 249  
Leu Leu Pro Gly Gln Gln Glu Ala Thr Gln Cys Val Glu Ala Gly Ala  
1 5 10 15  
Gly Glu Gly Ala Leu Thr Pro Met Cys Pro Cys Arg Gln Glu Gln Phe  
20 25 30  
Val Asp Leu Tyr Lys Glu Phe Glu Pro Ser Leu Val Asn Ser Thr Val  
35 40 45  
Tyr Ile Met Ala Met Ala Ile Gln Met Ala Pro Phe Ala Ile Asn Tyr  
50 55 60  
Lys Val Arg Pro Gly Pro Cys Xaa Asn Ile His Cys Leu Pro Thr Gln  
65 70 75 80  
Pro His Pro Met Lys Pro Ser Val Pro His Pro His Arg Ala Arg Pro  
85 90 95  
Ser Trp Arg Ala Cys Pro Arg Thr Ser Pro Trp Cys Gly Val Trp Gln  
100 105 110  
Phe His Ser Trp Pro Ser Leu Ala Cys Ser Ser Ala Pro Arg Pro Thr  
115 120 125  
Ser Thr Ala Ser Leu Ala Ser Trp Thr Ser Leu Trp Ser Ser Ser Trp  
130 135 140  
Ser Leu Pro Arg Ser Cys Ser Trp Thr Ser Ala Trp Arg Ser Trp Pro  
145 150 155 160

140

Thr Ala Ser Cys Ser Ser Trp Gly Pro Arg Ser  
 165 170

<210> 250  
 <211> 45  
 <212> PRT  
 <213> Homo sapiens

<400> 250  
 Leu Leu Pro Gly Gln Gln Glu Ala Thr Gln Cys Val Glu Ala Gly Ala  
 1 5 10 15

Gly Glu Gly Ala Leu Thr Pro Met Cys Pro Cys Arg Gln Glu Gln Phe  
 20 25 30

Val Asp Leu Tyr Lys Glu Phe Glu Pro Ser Leu Val Asn  
 35 40 45

<210> 251  
 <211> 44  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (27)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 251  
 Ser Thr Val Tyr Ile Met Ala Met Ala Ile Gln Met Ala Pro Phe Ala  
 1 5 10 15

Ile Asn Tyr Lys Val Arg Pro Gly Pro Cys Xaa Asn Ile His Cys Leu  
 20 25 30

Pro Thr Gln Pro His Pro Met Lys Pro Ser Val Pro  
 35 40

<210> 252  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<400> 252  
 His Pro His Arg Ala Arg Pro Ser Trp Arg Ala Cys Pro Arg Thr Ser  
 1 5 10 15

Pro Trp Cys Gly Val Trp Gln Phe His Ser Trp Pro Ser Leu Ala Cys  
 20 25 30

Ser Ser Ala Pro Arg Pro Thr Ser Thr Ala

141

35

40

<210> 253  
 <211> 41  
 <212> PRT  
 <213> Homo sapiens

<400> 253  
 Ser Leu Ala Ser Trp Thr Ser Leu Trp Ser Ser Ser Trp Ser Leu Pro  
 1 5 10 15  
 Arg Ser Cys Ser Trp Thr Ser Ala Trp Arg Ser Trp Pro Thr Ala Ser  
 20 25 30  
 Cys Ser Ser Ser Trp Gly Pro Arg Ser  
 35 40

<210> 254  
 <211> 48  
 <212> PRT  
 <213> Homo sapiens

<400> 254  
 Thr Arg Asn Ile Leu Ser Phe Ile Lys Cys Val Ile His Asn Phe Trp  
 1 5 10 15  
 Ile Pro Lys Glu Ser Asn Glu Ile Thr Ile Ile Ile Asn Pro Tyr Arg  
 20 25 30  
 Glu Thr Val Cys Phe Ser Val Glu Pro Val Lys Lys Ile Phe Asn Tyr  
 35 40 45

<210> 255  
 <211> 27  
 <212> PRT  
 <213> Homo sapiens

<400> 255  
 Leu Val Val Leu Phe Ala Ser Ser Asn Ser Arg Tyr Leu Lys Tyr Phe  
 1 5 10 15  
 Phe Leu Val Pro Leu Ile Leu Gly Ser Ala Trp  
 20 25

<210> 256  
 <211> 20  
 <212> PRT  
 <213> Homo sapiens

142

&lt;400&gt; 256

His Glu Trp Lys Cys Lys Gln Lys Tyr Ser Glu Gly Ser Gly Asn Thr  
1 5 10 15

Arg Ile Gly Asn  
20

&lt;210&gt; 257

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 257

Leu Leu Pro Leu Cys Phe Leu Gly Pro Arg Gln Val Leu Glu Glu Phe  
1 5 10 15

Pro Ser Ile Val  
20

&lt;210&gt; 258

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 258

Pro Thr Arg Pro Ser Lys His Gln Glu Ala Gly Ser  
1 5 10

&lt;210&gt; 259

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (39)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 259

Gly Gln Gly Pro Ala Gly Arg Trp Val Arg Arg Leu Pro Cys Ser Arg  
1 5 10 15

Arg Ala Gly Gly Glu Arg Gly Pro His Trp Gly Val Trp Ala Gly Pro  
20 25 30

Gln Met Ser Cys Gly Leu Xaa Phe Gly Pro  
35 40

&lt;210&gt; 260

&lt;211&gt; 193



143

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 260

Trp Arg Thr Gln Gly Pro Met Val Leu Leu Trp Val Val Thr Cys Pro  
 1 5 10 15  
 Ala Thr Met Leu Thr Glu Pro Gln Asn Pro His Leu Ile Gly Phe Val  
 20 25 30  
 Ala Tyr Ser Gly Pro Ser His Thr Thr Gln Pro His Lys Tyr Trp Leu  
 35 40 45  
 Leu Leu Asp Gly Gln Ala Asp Pro Ala Ala Ala Glu Gly Pro Val Lys  
 50 55 60  
 Arg Lys Ala Ala Ser Val Val Trp Trp Pro Gln Ala Leu Arg His Leu  
 65 70 75 80  
 Ser Leu Leu Val His Cys Trp Glu Glu Ser Tyr Glu Met Asn Ile Gly  
 85 90 95  
 Cys Gln Ser Leu Trp Ala Gly Gly Leu Ala Ser Ser Gly Asn Gly Trp  
 100 105 110  
 Asp Leu Gly Val Ala Phe Arg Arg Asp Thr Cys Met Ser Ser Ser Ser  
 115 120 125  
 Leu His Trp Lys Glu Phe Lys Tyr Ala Pro Gly Ser Leu His Tyr Phe  
 130 135 140  
 Ala Leu Ser Phe Val Leu Ile Leu Thr Glu Ile Cys Leu Val Ser Ser  
 145 150 155 160  
 Gly Met Gly Phe Pro Gln Glu Gly Lys His Phe Ser Val Leu Gly Ser  
 165 170 175  
 Pro Asp Cys Ser Leu Trp Gly Arg Asp Glu His Val Pro Arg Glu Phe  
 180 185 190

Ala

&lt;210&gt; 261

&lt;211&gt; 42

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 261

Trp Arg Thr Gln Gly Pro Met Val Leu Leu Trp Val Val Thr Cys Pro  
 1 5 10 15  
 Ala Thr Met Leu Thr Glu Pro Gln Asn Pro His Leu Ile Gly Phe Val  
 20 25 30

144

Ala Tyr Ser Gly Pro Ser His Thr Thr Gln  
                   35                                  40

&lt;210&gt; 262

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 262

Pro His Lys Tyr Trp Leu Leu Leu Asp Gly Gln Ala Asp Pro Ala Ala  
       1                                  5                                  10                                  15

Ala Glu Gly Pro Val Lys Arg Lys Ala Ala Ser Val Val Trp Trp Pro  
                   20                                  25                                  30

Gln Ala Leu Arg His Leu Ser Leu Leu  
                   35                                  40

&lt;210&gt; 263

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 263

Val His Cys Trp Glu Glu Ser Tyr Glu Met Asn Ile Gly Cys Gln Ser  
       1                                  5                                  10                                  15

Leu Trp Ala Gly Gly Leu Ala Ser Ser Gly Asn Gly Trp Asp Leu Gly  
                   20                                  25                                  30

Val Ala Phe Arg Arg Asp Thr Cys Met  
                   35                                  40

&lt;210&gt; 264

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 264

Ser Ser Ser Ser Leu His Trp Lys Glu Phe Lys Tyr Ala Pro Gly Ser  
       1                                  5                                  10                                  15

Leu His Tyr Phe Ala Leu Ser Phe Val Leu Ile Leu Thr Glu Ile Cys  
                   20                                  25                                  30

Leu Val Ser Ser Gly Met Gly Phe Pro Gln Glu Gly  
                   35                                  40

&lt;210&gt; 265

&lt;211&gt; 25

145

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 265

Lys His Phe Ser Val Leu Gly Ser Pro Asp Cys Ser Leu Trp Gly Arg  
 1 5 10 15

Asp Glu His Val Pro Arg Glu Phe Ala  
 20 25

&lt;210&gt; 266

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 266

Ile Ala Gln Gly Thr Val Pro Leu Thr Lys Arg Gly Val Gln Ser Ser  
 1 5 10 15

Gly Pro Asp Tyr Pro Glu Gly Thr Leu Thr Pro Leu Pro Arg Gly  
 20 25 30

&lt;210&gt; 267

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 267

Ile Ala Gln Gly Thr Val Pro Leu Thr Lys Arg Gly Val Gln Ser Ser  
 1 5 10 15

Gly Pro Asp Tyr Pro Glu Gly Thr Leu Thr Pro Leu Pro Arg Gly  
 20 25 30

&lt;210&gt; 268

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 268

Asp Cys Leu Tyr Leu Ala Leu Ser Phe Pro Trp His Cys His Cys His  
 1 5 10 15

His His Pro Pro Ser Gly Ser Leu Leu Tyr Pro Phe  
 20 25

&lt;210&gt; 269

&lt;211&gt; 101

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

146

&lt;400&gt; 269

Ala Ser Leu Pro Pro Ser Arg Ser Arg Pro Leu Ala Asn Met Ala Leu  
 1 5 10 15

Val Pro Cys Gln Val Leu Arg Met Ala Ile Leu Leu Ser Tyr Cys Ser  
 20 25 30

Ile Leu Cys Asn Tyr Lys Ala Ile Glu Met Pro Ser His Gln Thr Tyr  
 35 40 45

Gly Gly Ser Trp Lys Phe Leu Thr Phe Ile Asp Leu Val Ile Gln Ala  
 50 55 60

Val Phe Phe Gly Ile Cys Val Leu Thr Asp Leu Ser Ser Leu Leu Thr  
 65 70 75 80

Arg Gly Ser Gly Asn Gln Glu Gln Glu Arg Gln Leu Lys Lys Leu Ile  
 85 90 95

Ser Leu Arg Asp Trp  
 100

&lt;210&gt; 270

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 270

Met Ser Arg Ser Ser Arg Ile Ser Gly Leu Ser Cys Pro Trp Leu Leu  
 1 5 10 15

&lt;210&gt; 271

&lt;211&gt; 45

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 271

Asp His Trp Pro Ala Gly Phe Leu Pro Pro Ala Pro Gly Leu Lys Phe  
 1 5 10 15

Pro Val Ala Leu Glu Val Phe Arg Lys Val Leu Pro Ala Val Cys Pro  
 20 25 30

Thr Asp Cys Ser Gly Ser Ala Gly Lys Glu Arg Asn Ser  
 35 40 45

&lt;210&gt; 272

&lt;211&gt; 47

&lt;212&gt; PRT

147

&lt;213&gt; Homo sapiens

&lt;400&gt; 272

Glu Glu Ile Ala Thr Ser Ile Glu Pro Ile Arg Asp Phe Leu Ala Ile  
1 5 10 15  
Val Phe Phe Ala Ser Ile Gly Leu His Val Phe Pro Thr Phe Val Ala  
20 25 30  
Tyr Glu Leu Thr Val Leu Val Phe Leu Thr Leu Ser Val Val Val  
35 40 45

&lt;210&gt; 273

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 273

Tyr Cys Asn Leu Gln Cys Arg  
1 5

&lt;210&gt; 274

&lt;211&gt; 44

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 274

Ser Ala Leu Ile Gly Asn Pro Lys Gly Cys Phe Gly Cys Phe Ser Pro  
1 5 10 15  
Val Val Leu Arg Glu Trp Ser Val Glu Ser Trp Lys Ser Leu Arg Pro  
20 25 30  
Phe Gln Ala Ile Cys Lys Leu Lys Thr Asn Phe Arg  
35 40

&lt;210&gt; 275

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 275

His Glu Ala Ala Leu Arg Gly Pro  
1 5

&lt;210&gt; 276

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 276

148

Ser Asn Ala Ala Gly Asn Val Val Arg Ala Phe Leu Tyr Ile Asn His  
 1 5 10 15

Leu Lys Leu Gly Cys Lys Val Gly Leu Ala  
 20 25

&lt;210&gt; 277

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 277

Asn Trp Ala Val Leu Asn Met Leu Leu Ser Lys Gly Lys Ile Thr Ile  
 1 5 10 15

Phe Leu Gly Pro Leu Glu Cys Gly Ser  
 20 25

&lt;210&gt; 278

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 278

Pro Ser His Gln Thr Arg Lys Gly Lys Ser Ala Lys Leu Leu Asp Arg  
 1 5 10 15

Pro Pro Glu Ala Leu Arg Met Lys Ile Ile Thr Thr Thr Leu Leu Leu  
 20 25 30

Ala Cys His Leu Gln Leu Glu Val Gly Val Val Val Gly Gly Glu Val  
 35 40 45

Asp

&lt;210&gt; 279

&lt;211&gt; 51

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 279

Phe Gln Ala Ser Ser Ala Asn Asn Gln Gln Asn Trp Gly Ser Gln Pro  
 1 5 10 15

Ile Ala Gln Gln Pro Leu Gln Gln Gly Gly Asp Tyr Ser Gly Asn Tyr  
 20 25 30

Gly Tyr Asn Asn Asp Asn Gln Glu Phe Tyr Gln Asp Thr Tyr Gly Gln  
 35 40 45

Gln Trp Lys

50

<210> 280  
 <211> 264  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (2)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (6)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (14)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 280  
 Trp Xaa Pro Leu Leu Xaa Thr Ser Gly Ser Pro Gly Leu Xaa Gly Phe  
   1                  5                  10                  15  
 Gly Thr Arg Met Asn Gly Lys Glu Ile Glu Gly Glu Glu Ile Glu Ile  
                   20                  25                  30  
 Val Leu Ala Lys Pro Pro Asp Lys Lys Arg Lys Glu Arg Gln Ala Ala  
           35                  40                  45  
 Arg Gln Ala Ser Arg Ser Thr Ala Tyr Glu Asp Tyr Tyr Tyr His Pro  
   50                  55                  60  
 Pro Pro Arg Met Pro Pro Pro Ile Arg Gly Arg Gly Arg Gly Gly Gly  
   65                  70                  75                  80  
 Arg Gly Gly Tyr Gly Tyr Pro Pro Asp Tyr Tyr Gly Tyr Glu Asp Tyr  
                   85                  90                  95  
 Tyr Asp Asp Tyr Tyr Gly Tyr Asp Tyr His Asp Tyr Arg Gly Gly Tyr  
           100                  105                  110  
 Glu Asp Pro Tyr Tyr Gly Tyr Asp Asp Gly Tyr Ala Val Arg Gly Arg  
   115                  120                  125  
 Gly Gly Gly Arg Gly Gly Arg Gly Ala Pro Pro Pro Pro Arg Gly Arg  
   130                  135                  140  
 Gly Ala Pro Pro Pro Arg Gly Arg Ala Gly Tyr Ser Gln Arg Gly Ala  
   145                  150                  155                  160  
 Pro Leu Gly Pro Pro Arg Gly Ser Arg Gly Gly Arg Gly Gly Pro Ala

150

	165		170		175
Gln Gln Gln Arg Gly Arg Gly Ser Arg Gly Ser Arg Gly Asn Arg Gly					
	180		185		190
Gly Asn Val Gly Gly Lys Arg Lys Ala Asp Gly Tyr Asn Gln Pro Asp					
	195		200		205
Ser Lys Arg Arg Gln Pro Thr Thr Asn Arg Thr Gly Val Pro Asn Pro					
	210		215		220
Ser Leu Ser Ser Arg Phe Ser Lys Val Val Thr Ile Leu Val Thr Met					
	225		230		235
Val Thr Ile Met Thr Thr Arg Asn Phe Ile Arg Ile Leu Met Gly Asn					
	245		250		255
Ser Gly Ser Arg Gln Val Arg Ala					
	260				

&lt;210&gt; 281

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 281

Arg Met Asn Gly Lys Glu Ile Glu Gly Glu Glu Ile Glu Ile Val Leu
1 5 10 15

Ala Lys Pro Pro Asp Lys Lys Arg Lys Glu Arg
20 25

&lt;210&gt; 282

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 282

Tyr Tyr His Pro Pro Pro Arg Met Pro Pro Pro Ile Arg Gly Arg Gly
1 5 10 15

Arg Gly Gly Gly Arg Gly Gly Tyr Gly
20 25

&lt;210&gt; 283

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 283

Asp Tyr Arg Gly Gly Tyr Glu Asp Pro Tyr Tyr Gly Tyr Asp Asp Gly
1 5 10 15



Tyr Ala Val Arg Gly Arg Gly Gly Arg  
20 25

<210> 284  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 284  
Pro Pro Pro Arg Gly Arg Ala Gly Tyr Ser Gln Arg Gly Ala Pro Leu  
1 5 10 15

Gly Pro Pro Arg Gly Ser Arg Gly Gly Arg Gly Gly  
20 25

<210> 285  
<211> 35  
<212> PRT  
<213> Homo sapiens

<400> 285  
Ala Asp Gly Tyr Asn Gln Pro Asp Ser Lys Arg Arg Gln Pro Thr Thr  
1 5 10 15

Asn Arg Thr Gly Val Pro Asn Pro Ser Leu Ser Ser Arg Phe Ser Lys  
20 25 30

Val Val Thr  
35

<210> 286  
<211> 19  
<212> PRT  
<213> Homo sapiens

<400> 286  
Leu Gln Ile Pro Pro Ser Ser Gln Ser Leu Gly Leu Lys Asn Ala Asp  
1 5 10 15

Ser Ser Ile

<210> 287  
<211> 129  
<212> PRT  
<213> Homo sapiens

<400> 287  
Gly Gly Pro Pro Glu Ser Ala Pro Trp Leu Pro Ala Val Leu Arg Ala  
1 5 10 15

152

Pro Val Leu Thr Ser Arg Cys Ala Ser Ser Asp Ser Glu Gly Pro Val  
                   20                  25                  30

Trp Phe Cys Gln Pro Gly Ser Gly Pro Ser Ser Thr Glu Met Ser Cys  
                   35                  40                  45

His Cys Ile Leu Gly Pro Gly Ser Ser Cys Leu Cys Val Leu Arg Gly  
                   50                  55                  60

Ser Met Trp Thr Pro Ser Val Pro Gly Trp Pro Gln Pro Ala Lys Glu  
                   65                  70                  75                  80

Thr Gly Ala Ser Ser Cys Ser Val Phe Ser Ala Asn Asn Gly Ser Cys  
                                   85                  90                  95

Pro Leu Pro Leu His Asn His Gln Arg Gln Ala Ser Leu Asp Thr Gly  
                   100                  105                  110

Leu Ser Leu Glu His Val Pro Gly Glu Ser Tyr Phe Tyr Ser Pro Val  
                   115                  120                  125

Gly

&lt;210&gt; 288

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 288

Ser Ser Asp Ser Glu Gly Pro Val Trp Phe Cys Gln Pro Gly Ser Gly  
   1                  5                  10                  15

Pro Ser Ser Thr Glu Met Ser Cys His Cys Ile Leu Gly Pro Gly Ser  
                   20                  25                  30

Ser Cys

&lt;210&gt; 289

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 289

Trp Thr Pro Ser Val Pro Gly Trp Pro Gln Pro Ala Lys Glu Thr Gly  
   1                  5                  10                  15

Ala Ser Ser Cys Ser Val Phe Ser Ala Asn Asn Gly  
                   20                  25

<210> 290  
<211> 21  
<212> PRT  
<213> Homo sapiens

<400> 290  
Gln Arg Gln Ala Ser Leu Asp Thr Gly Leu Ser Leu Glu His Val Pro  
1 5 10 15

Gly Glu Ser Tyr Phe  
20

<210> 291  
<211> 29  
<212> PRT  
<213> Homo sapiens

<400> 291  
Ser Ser Ser Leu Val Leu Thr Ile Arg Ser Gln Thr Leu Phe Leu Ala  
1 5 10 15

Ser Phe Ile His Ser Thr Ser Ile Phe Cys Ala Leu Asn  
20 25

<210> 292  
<211> 12  
<212> PRT  
<213> Homo sapiens

<400> 292  
Cys Cys Cys Arg Leu Gly Leu Ser Gly Pro Lys Cys  
1 5 10

<210> 293  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 293  
Arg Ala Phe Trp Gly Leu Gly Ala Leu Gln Leu Leu Asp Leu Ser Ala  
1 5 10 15

Asn Gln Leu Glu Ala Leu  
20

<210> 294  
<211> 34  
<212> PRT  
<213> Homo sapiens

<400> 294

154

His Ala Ser Gly Arg Arg Thr Gly Ser Ala Asp Asp Gly Leu Gln Gly  
 1 5 10 15

Arg Thr Gly Ser Gly Pro Pro Thr Ala Gly Ala Gly Gly Gly Gly Ala  
 20 25 30

Ala Pro

<210> 295

<211> 205

<212> PRT

<213> Homo sapiens

<400> 295

Val Ser Ala Ala Ala Gly Ala Arg Leu Ala Pro Arg Ala Pro Gly Ala  
 1 5 10 15

Pro Ala Gly Cys Arg Pro Met Arg Gly Cys Ala Ala Arg Ala Ala Ala  
 20 25 30

Arg Lys Ser Leu Val Pro Val Leu Pro Ala Gly Trp Arg Ser Gly Pro  
 35 40 45

Ala Ala Ala Ala Arg Pro Gly Pro Arg Arg Leu Ala His Ala Pro Ser  
 50 55 60

Ala Ala Arg Ser Arg Ala Gly Pro Gly Ala Val Ala Arg Pro Leu Pro  
 65 70 75 80

Arg Arg His Leu Ala Ala Ala His Gly Arg Gly Cys Gly Pro Ala Ala  
 85 90 95

Ala Arg Ala Gly Ala Gly Ser Gly Pro Gly Ala Arg Arg Ala Ala Arg  
 100 105 110

Val Pro Thr Ala Gly Arg Pro Pro Gly Thr His Val His Thr Ser Gly  
 115 120 125

Gln Ser Gly Ala Pro Arg Asp Pro Glu Gly Glu Ala Leu Ala Asp Thr  
 130 135 140

Trp Ala Gln Thr Gly Gln Gly Asp Ser Ser Ser Asn Ser Ser Ser Ser  
 145 150 155 160

Gly Arg Gly Arg Asp Gln Glu Gly Pro Arg Met Gly Ala Ala Pro Pro  
 165 170 175

Pro Pro Ala Pro Ala Val Gly Gly Pro Leu Pro Val Arg Pro Trp Ser  
 180 185 190

Pro Ser Ser Ala Glu Pro Val Leu Arg Pro Asp Ala Trp  
 195 200 205

<210> 296  
 <211> 368  
 <212> PRT  
 <213> Homo sapiens

<400> 296

Thr Arg Pro Ala Ala Glu Arg Ala Pro Arg Thr Thr Gly Ser Arg Asp  
 1 5 10 15

Ala Gln Ala Ala Gly Leu Pro Pro Arg Val Pro Gly Ala Gly Gly Leu  
 20 25 30

Pro Pro Cys Gly Ala Leu Pro Gly Arg Gly Leu Gly Arg Cys Cys Cys  
 35 40 45

Cys Cys Cys Cys Cys Arg Leu Gly Leu Ser Gly Pro Lys Cys Arg Pro  
 50 55 60

Gly Pro Arg Pro Arg Gly Pro Trp Ala Pro Arg Thr Ala Pro Arg Cys  
 65 70 75 80

Ala Arg Ala Cys Arg Glu Ala Cys Gln Leu Ser Ala Leu Ser Leu Pro  
 85 90 95

Ala Val Pro Pro Gly Leu Ser Leu Arg Leu Arg Ala Leu Leu Leu Asp  
 100 105 110

His Asn Arg Val Arg Ala Leu Pro Pro Gly Ala Phe Ala Gly Ala Gly  
 115 120 125

Ala Leu Gln Arg Leu Asp Leu Arg Glu Asn Gly Leu His Ser Val His  
 130 135 140

Val Arg Ala Phe Trp Gly Leu Gly Ala Leu Gln Leu Leu Asp Leu Ser  
 145 150 155 160

Ala Asn Gln Leu Glu Ala Leu Ala Pro Gly Thr Phe Ala Pro Leu Arg  
 165 170 175

Ala Leu Arg Asn Leu Ser Leu Ala Gly Asn Arg Leu Ala Arg Leu Glu  
 180 185 190

Pro Ala Ala Leu Gly Ala Leu Pro Leu Leu Arg Ser Leu Ser Leu Gln  
 195 200 205

Asp Asn Glu Leu Ala Ala Leu Ala Pro Gly Leu Leu Gly Arg Leu Pro  
 210 215 220

Ala Leu Asp Ala Leu His Leu Arg Gly Asn Pro Trp Gly Cys Gly Cys  
 225 230 235 240

Ala Leu Arg Pro Leu Cys Ala Trp Leu Arg Arg His Pro Leu Pro Ala  
 245 250 255

156

Ser Glu Ala Glu Thr Val Leu Cys Val Trp Pro Gly Arg Leu Thr Leu  
                   260                                  265                                  270

Ser Pro Leu Thr Ala Phe Ser Asp Ala Ala Phe Ser His Cys Ala Gln  
                   275                                  280                                  285

Pro Leu Ala Leu Arg Asp Leu Ala Arg Gly Leu His Ala Arg Ala Gly  
                   290                                  295                                  300

Leu Leu Pro Arg Gln Pro Gly Phe Leu Pro Gly Ala Gly Leu Trp Ala  
                   305                                  310                                  315                                  320

His Arg Leu Pro Cys Ala Pro Pro Pro Pro Pro His Arg Arg Pro Pro  
                                   325                                  330                                  335

Pro Ala Glu Thr Val Gln Thr Arg Thr Pro Ile Pro Thr Pro Thr Ala  
                   340                                  345                                  350

Val Pro Arg Pro Arg Thr Arg Gly Ala Pro Ser Ala Ala Ala Gln Ala  
                   355                                  360                                  365

<210> 297  
 <211> 47  
 <212> PRT  
 <213> Homo sapiens

<400> 297  
 Gly Cys Arg Pro Met Arg Gly Cys Ala Ala Arg Ala Ala Arg Lys  
           1                                  5                                  10                                  15

Ser Leu Val Pro Val Leu Pro Ala Gly Trp Arg Ser Gly Pro Ala Ala  
                   20                                  25                                  30

Ala Ala Arg Pro Gly Pro Arg Arg Leu Ala His Ala Pro Ser Ala  
                   35                                  40                                  45

<210> 298  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

<400> 298  
 Pro Gly Ala Val Ala Arg Pro Leu Pro Arg Arg His Leu Ala Ala Ala  
           1                                  5                                  10                                  15

His Gly Arg Gly Cys Gly Pro Ala Ala Ala Arg Ala Gly Ala  
                   20                                  25                                  30

<210> 299

<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 299  
Ser Gly Gln Ser Gly Ala Pro Arg Asp Pro Glu Gly Glu Ala Leu Ala  
1 5 10 15

Asp Thr Trp Ala Gln Thr Gly Gln  
20

<210> 300  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 300  
Pro Pro Ala Pro Ala Val Gly Gly Pro Leu Pro Val Arg Pro Trp Ser  
1 5 10 15

Pro Ser Ser Ala Glu Pro Val  
20

<210> 301  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 301  
Ala Pro Arg Thr Thr Gly Ser Arg Asp Ala Gln Ala Ala Gly Leu Pro  
1 5 10 15

Pro Arg Val Pro Gly Ala Gly Gly Leu Pro  
20 25

<210> 302  
<211> 22  
<212> PRT  
<213> Homo sapiens

<400> 302  
Gly Pro Arg Pro Arg Gly Pro Trp Ala Pro Arg Thr Ala Pro Arg Cys  
1 5 10 15

Ala Arg Ala Cys Arg Glu  
20

<210> 303  
<211> 31  
<212> PRT  
<213> Homo sapiens

&lt;400&gt; 303

Ala Val Pro Pro Gly Leu Ser Leu Arg Leu Arg Ala Leu Leu Leu Asp  
1 5 10 15

His Asn Arg Val Arg Ala Leu Pro Pro Gly Ala Phe Ala Gly Ala  
20 25 30

&lt;210&gt; 304

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 304

Leu Gly Ala Leu Gln Leu Leu Asp Leu Ser Ala Asn Gln Leu Glu Ala  
1 5 10 15

Leu Ala Pro Gly Thr Phe Ala Pro  
20

&lt;210&gt; 305

&lt;211&gt; 36

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 305

Pro Pro Gly Ala Phe Ala Gly Ala Gly Ala Leu Gln Arg Leu Asp Leu  
1 5 10 15

Arg Glu Asn Gly Leu His Ser Val His Val Arg Ala Phe Trp Gly Leu  
20 25 30

Gly Ala Leu Gln  
35

&lt;210&gt; 306

&lt;211&gt; 28

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 306

Arg Asn Leu Ser Leu Ala Gly Asn Arg Leu Ala Arg Leu Glu Pro Ala  
1 5 10 15

Ala Leu Gly Ala Leu Pro Leu Leu Arg Ser Leu Ser  
20 25

&lt;210&gt; 307

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens



159

&lt;400&gt; 307

Leu Pro Ala Leu Asp Ala Leu His Leu Arg Gly Asn Pro Trp Gly Cys  
1 5 10 15

Gly Cys Ala Leu Arg Pro Leu Cys Ala Trp  
20 25

&lt;210&gt; 308

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 308

Thr Val Leu Cys Val Trp Pro Gly Arg Leu Thr Leu Ser Pro Leu Thr  
1 5 10 15

Ala Phe Ser Asp Ala Ala Phe Ser His Cys Ala Gln Pro Leu Ala Leu  
20 25 30

Arg Asp

&lt;210&gt; 309

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 309

Leu His Ala Arg Ala Gly Leu Leu Pro Arg Gln Pro Gly Phe Leu Pro  
1 5 10 15

Gly Ala Gly Leu Trp Ala His Arg  
20

&lt;210&gt; 310

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 310

Thr Val Gln Thr Arg Thr Pro Ile Pro Thr Pro Thr Ala Val Pro Arg  
1 5 10 15

Pro Arg Thr Arg Gly Ala Pro Ser  
20

&lt;210&gt; 311

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

160

&lt;400&gt; 311

His Ala Ser Gly Arg Pro Asp Arg Ser Ser Ala Pro Ile Gly Asn Ser  
1 5 10 15

Gly Leu Pro Cys Pro Asp Leu Glu Pro Leu Gly Gly Leu Gln Ser Lys  
20 25 30

Cys Arg Leu Cys Ala Pro Thr Glu Ala Arg Gly Leu Trp Ser Arg Ser  
35 40 45

Leu Cys Ser Asp Arg Cys Asp Thr Trp Arg Ser  
50 55

&lt;210&gt; 312

&lt;211&gt; 29

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 312

Gly Leu Pro Cys Pro Asp Leu Glu Pro Leu Gly Gly Leu Gln Ser Lys  
1 5 10 15

Cys Arg Leu Cys Ala Pro Thr Glu Ala Arg Gly Leu Trp  
20 25

&lt;210&gt; 313

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 313

Gln Glu Trp Glu Ser Glu Leu Gly Glu Arg Arg Lys Pro Leu Gln Ala  
1 5 10 15

&lt;210&gt; 314

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 314

Cys Gln Ser Ser Asn Leu Ile Phe Phe Gln Phe Val Asn Ile Leu Phe  
1 5 10 15

Asn Leu Met Met Asp Ile Leu Val Asp Phe Ser Ile Thr Lys Met Pro  
20 25 30

Ile Asn Ser Ile Phe Ser Leu Tyr Phe Cys Tyr Glu Ile Ile  
35 40 45

161

<210> 315  
 <211> 134  
 <212> PRT  
 <213> Homo sapiens

<400> 315

Gly	Pro	Val	Trp	Leu	Phe	Cys	Phe	Leu	Thr	Leu	Cys	Arg	Lys	Pro	Ser
1				5					10					15	
Gln	Leu	Phe	Ser	Gln	Glu	Asn	Ser	Cys	Met	Asp	Val	Ala	Gly	Gly	Val
			20					25					30		
Thr	Thr	Cys	Leu	Pro	Pro	Trp	Phe	Ser	Arg	Gly	Ala	Pro	Ala	Gln	Met
		35					40					45			
Ser	Gln	Trp	Pro	Pro	Ser	Ser	Asp	His	Gly	Ala	Val	Arg	Ala	Gly	Arg
	50					55					60				
Asp	Ser	Arg	Val	Gly	Pro	Val	Gln	Pro	Ser	His	Leu	Thr	Cys	Glu	Gly
65					70					75				80	
Gly	Lys	Glu	Glu	Arg	Glu	Lys	Asn	Lys	Lys	Ala	Glu	Val	Asn	Pro	Pro
				85					90					95	
Thr	Gly	Met	Gly	Leu	Ala	Asn	Arg	Ile	Pro	Arg	Asp	Asp	Ile	Thr	Leu
			100					105					110		
Lys	Leu	Arg	Asn	Gln	Gly	Lys	Leu	Arg	Thr	Lys	Glu	Asn	Arg	Thr	Gln
	115						120					125			
Ser	Ala	Lys	Arg	His	Pro										
					130										

<210> 316  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<400> 316

Val	Ala	Cys	Lys	Pro	Glu	Asn	Arg	Thr	Lys	Thr	His	Phe	Ala	Ser	Ser
1				5					10					15	
Pro	Ala	Cys	Asp	Gly	His	Ala	Leu	Gly	Gly	Gln	Val	Gly	Phe	Ala	Ile
			20					25					30		
Cys	Phe	Leu	Ser	Cys	Leu	Phe	Pro	Pro	Met						
		35					40								

<210> 317  
 <211> 40  
 <212> PRT

162

&lt;213&gt; Homo sapiens

&lt;400&gt; 317

Ser His Pro Met Pro Asn Thr Pro Gln Lys Gln Leu Leu Phe Ser Glu  
 1 5 10 15

Asp Asn Glu Leu Leu Val Ser Leu Arg Thr Gly Arg Lys Pro Thr Leu  
 20 25 30

Gln Ala Ala Leu Arg Val Thr Gly  
 35 40

&lt;210&gt; 318

&lt;211&gt; 59

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (26)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 318

Glu Gly Asp Pro Arg Gly Arg Pro Arg Pro Arg Pro Leu Gly Pro Pro  
 1 5 10 15

Pro Gln Leu Thr Leu Pro Thr Ala Leu Xaa Asp Ile Leu Arg Gln Val  
 20 25 30

Arg Ala Pro Gly Leu Arg Leu Ser Arg Ala Leu Glu Val Gly Arg Lys  
 35 40 45

Gly Ser Pro Ile Phe Lys Ile Gln Ile Tyr Leu  
 50 55

&lt;210&gt; 319

&lt;211&gt; 250

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (145)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 319

Ala His Arg Leu Gln Ile Arg Leu Leu Thr Trp Asp Val Lys Asp Thr  
 1 5 10 15

Leu Leu Arg Leu Arg His Pro Leu Gly Glu Ala Tyr Ala Thr Lys Ala  
 20 25 30

Arg Ala His Gly Leu Glu Val Glu Pro Ser Ala Leu Glu Gln Gly Phe

163

35	40	45
Arg Gln Ala Tyr Arg Ala Gln Ser His Ser Phe Pro Asn Tyr Gly Leu		
50	55	60
Ser His Gly Leu Thr Ser Arg Gln Trp Trp Leu Asp Val Val Leu Gln		
65	70	75
Thr Phe His Leu Ala Gly Val Gln Asp Ala Gln Ala Val Ala Pro Ile		
85	90	95
Ala Glu Gln Leu Tyr Lys Asp Phe Ser His Pro Cys Thr Trp Gln Val		
100	105	110
Leu Asp Gly Ala Glu Asp Thr Leu Arg Glu Cys Arg Thr Arg Gly Leu		
115	120	125
Arg Leu Ala Val Ile Ser Asn Phe Asp Arg Arg Leu Glu Gly Ile Leu		
130	135	140
Xaa Gly Leu Gly Leu Arg Glu His Phe Asp Phe Val Leu Thr Ser Glu		
145	150	155
Ala Ala Gly Trp Pro Lys Pro Asp Pro Arg Ile Phe Gln Glu Ala Leu		
165	170	175
Arg Leu Ala His Met Glu Pro Val Val Ala Ala His Val Gly Asp Asn		
180	185	190
Tyr Leu Cys Asp Tyr Gln Gly Pro Arg Ala Val Gly Met His Ser Phe		
195	200	205
Leu Val Val Gly Pro Gln Ala Leu Asp Pro Val Val Arg Asp Ser Val		
210	215	220
Pro Lys Glu His Ile Leu Pro Ser Leu Ala His Leu Leu Pro Ala Leu		
225	230	235
Asp Cys Leu Glu Gly Ser Thr Pro Gly Leu		
245	250	

&lt;210&gt; 320

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 320

Ile Arg Leu Leu Thr Trp Asp Val Lys Asp Thr Leu Leu Arg Leu Arg
1 5 10 15

His Pro Leu Gly Glu Ala Tyr Ala Thr Lys Ala
20 25

164

<210> 321  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 321  
Leu Glu Gln Gly Phe Arg Gln Ala Tyr Arg Ala Gln Ser His Ser Phe  
1 5 10 15  
Pro Asn Tyr Gly Leu Ser His Gly  
20

<210> 322  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 322  
His Leu Ala Gly Val Gln Asp Ala Gln Ala Val Ala Pro Ile Ala Glu  
1 5 10 15  
Gln Leu Tyr Lys Asp Phe Ser His Pro Cys  
20 25

<210> 323  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 323  
Val Leu Asp Gly Ala Glu Asp Thr Leu Arg Glu Cys Arg Thr Arg Gly  
1 5 10 15  
Leu Arg Leu Ala Val Ile Ser  
20

<210> 324  
<211> 26  
<212> PRT  
<213> Homo sapiens

<400> 324  
Arg Glu His Phe Asp Phe Val Leu Thr Ser Glu Ala Ala Gly Trp Pro  
1 5 10 15  
Lys Pro Asp Pro Arg Ile Phe Gln Glu Ala  
20 25

<210> 325  
<211> 28  
<212> PRT

165

&lt;213&gt; Homo sapiens

&lt;400&gt; 325

Glu Pro Val Val Ala Ala His Val Gly Asp Asn Tyr Leu Cys Asp Tyr  
1 5 10 15

Gln Gly Pro Arg Ala Val Gly Met His Ser Phe Leu  
20 25

&lt;210&gt; 326

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 326

Val Val Arg Asp Ser Val Pro Lys Glu His Ile Leu Pro Ser Leu Ala  
1 5 10 15

His Leu Leu Pro Ala Leu Asp  
20

&lt;210&gt; 327

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 327

Ile Arg Lys Leu Gly Pro Gly Leu Ala Pro Cys Ser Cys Arg Ser Gly  
1 5 10 15

Gln Val Phe Pro Arg Val  
20

&lt;210&gt; 328

&lt;211&gt; 241

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 328

Lys Pro Leu Arg Met Ala Arg Pro Gly Gly Pro Glu His Asn Glu Tyr  
1 5 10 15

Ala Leu Val Ser Ala Trp His Ser Ser Gly Ser Tyr Leu Asp Ser Glu  
20 25 30

Gly Leu Arg His Gln Asp Asp Phe Asp Val Ser Leu Leu Val Cys His  
35 40 45

Cys Ala Ala Pro Phe Glu Glu Gln Gly Glu Ala Glu Arg His Val Leu  
50 55 60

Arg Leu Gln Phe Phe Val Val Leu Thr Ser Gln Arg Glu Leu Phe Pro

```
<210> 329
<211> 30
<212> PRT
<213> Homo sapiens
```

```

<400> 329
Ala Arg Gly Thr Leu Glu Leu Pro Thr Pro Leu Ile Ala Ala His Gln
  1             5             10             15

Leu Tyr Asn Tyr Val Ala Asp His Ala Ser Ser Tyr His Met
          20             25             30

```

```
<210> 330
<211> 37
<212> PRT
<213> Homo sapiens

<400> 330
```



167

Ser His Cys Glu Trp Pro Gly Gln Gly Ala Gln Asn Thr Thr Ser Met  
 1 5 10 15

Pro Trp Cys Arg His Gly Thr Val Leu Ala Pro Thr Trp Thr Leu Arg  
 20 25 30

Asp Phe Asp Thr Arg  
 35

<210> 331

<211> 91

<212> PRT

<213> Homo sapiens

<400> 331

Pro Leu Thr Thr Val Ser His Leu Cys Pro Leu Ser Leu Arg Val Phe  
 1 5 10 15

Thr Ser His Leu Asp Ile Thr Ala Gly His Ser His Arg Asp Asp Thr  
 20 25 30

Trp Val Pro Ile Pro Ala Leu Pro Leu Lys His Leu Arg Pro Pro Ser  
 35 40 45

Ser Pro Phe Ala Leu Gly Pro Trp Val Ser His Pro Leu Met Arg Trp  
 50 55 60

Val Gln Lys Leu Ser His Leu His Ser Asn Pro Gly Thr Gly Phe Ser  
 65 70 75 80

Met Gly Gly Lys Ser Ala Glu Lys Leu Lys Cys  
 85 90

<210> 332

<211> 179

<212> PRT

<213> Homo sapiens

<400> 332

Ser Thr Ala Ala Arg Gly Ala Pro Gly Pro Gly Arg Ala Gly Gly Thr  
 1 5 10 15

Pro Arg Ser Ser Pro Cys Gln Ile His Trp Gly His Arg Pro Pro Ala  
 20 25 30

Gly Leu Leu Pro Ile His Asp Gly Leu Leu Val Pro Glu Pro Asp Gln  
 35 40 45

Ser Ser Pro Lys Pro Leu Pro Gln Ser Cys Arg His Phe Gln Ser Pro  
 50 55 60

Asp Leu Gly Thr Gln Tyr Leu Val Ala Leu Asn Gln Lys Phe Thr Asp  
 65 70 75 80

168

Cys Ser Ala Leu Val Phe Trp Thr Pro Leu Arg Lys Asp Val Ser Glu  
                     85                    90                    95  
 Val Val Phe Arg Glu Ala Leu Pro Val Gln Pro Gln Asp Thr Arg Ser  
                     100                    105                    110  
 Pro Pro Ala Gln Leu Val Ser Thr Tyr His His Leu Glu Ser Val Ile  
                     115                    120                    125  
 Asn Thr Ala Cys Phe Thr Leu Leu Asp Pro Pro Pro Leu Lys Gly Val  
                     130                    135                    140  
 Asp Trp Thr Thr Glu Cys His Cys Ser Leu Asn His Gly Pro Thr Arg  
                     145                    150                    155                    160  
 Leu Pro Ala Arg Gly Arg Thr Asp Gln Pro Phe Trp Ala Pro Gly Gln  
                     165                    170                    175  
 Ala Arg His

<210> 333  
 <211> 56  
 <212> PRT  
 <213> Homo sapiens

<400> 333  
 His Gln Arg Leu Cys Asn Tyr Val Leu Arg Val Cys Cys Pro Ser Leu  
   1                    5                    10                    15  
 Ala Ala Gly Thr Ala Leu Pro Lys His Pro Gln Pro Leu Thr His Pro  
                     20                    25                    30  
 Gly Leu Gln Arg Val Arg Ser Thr Pro Arg Thr Pro Trp Ala Leu Leu  
                     35                    40                    45  
 Gly Tyr Ser Phe Arg Pro Pro Trp  
                     50                    55

<210> 334  
 <211> 28  
 <212> PRT  
 <213> Homo sapiens

<400> 334  
 Pro Gly Gly Pro Glu His Asn Glu Tyr Ala Leu Val Ser Ala Trp His  
   1                    5                    10                    15  
 Ser Ser Gly Ser Tyr Leu Asp Ser Glu Gly Leu Arg  
                     20                    25

169

<210> 335  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 335  
Asp Val Ser Leu Leu Val Cys His Cys Ala Ala Pro Phe Glu Glu Gln  
1 5 10 15  
Gly Glu Ala Glu Arg His Val Leu Arg  
20 25

<210> 336  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 336  
Arg Leu Thr Ala Asp Met Arg Arg Phe Arg Lys Pro Pro Arg Leu Pro  
1 5 10 15  
Pro Glu Pro Glu Ala Pro Gly Ser Ser Ala Gly Ser  
20 25

<210> 337  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 337  
Gly Glu Ala Ser Gly Leu Ile Leu Ala Pro Gly Pro Ala Pro Leu Phe  
1 5 10 15  
Pro Pro Leu Ala Ala Glu Val Gly Met  
20 25

<210> 338  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 338  
Thr Leu Trp Lys Arg Leu Phe Leu Leu Glu Pro Pro Gly Pro Asp Arg  
1 5 10 15  
Leu Arg Leu Gly Gly Arg Leu  
20

<210> 339  
<211> 28  
<212> PRT

170

&lt;213&gt; Homo sapiens

&lt;400&gt; 339

Leu Ala Glu Leu Glu Glu Leu Leu Glu Ala Val His Ala Lys Ser Ile  
 1 5 10 15

Gly Asp Ile Asp Pro Gln Leu Asp Cys Phe Leu Ser  
 20 25

&lt;210&gt; 340

&lt;211&gt; 197

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (97)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 340

Phe Gln Leu Tyr Phe Asn Pro Glu Leu Ile Phe Lys His Phe Gln Ile  
 1 5 10 15

Trp Arg Leu Ile Thr Asn Phe Leu Phe Phe Gly Pro Val Gly Phe Asn  
 20 25 30

Phe Leu Phe Asn Met Ile Phe Leu Tyr Arg Tyr Cys Arg Met Leu Glu  
 35 40 45

Glu Gly Ser Phe Arg Gly Arg Thr Ala Asp Phe Val Phe Met Phe Leu  
 50 55 60

Phe Gly Gly Phe Leu Met Thr Leu Phe Gly Leu Phe Val Ser Leu Val  
 65 70 75 80

Phe Leu Gly Gln Ala Phe Thr Ile Met Leu Val Tyr Val Trp Ser Arg  
 85 90 95

Xaa Asn Pro Tyr Val Arg Met Asn Phe Phe Gly Leu Leu Asn Phe Gln  
 100 105 110

Ala Pro Phe Leu Pro Trp Val Leu Met Gly Phe Ser Leu Leu Leu Gly  
 115 120 125

Asn Ser Ile Ile Val Asp Leu Leu Gly Ile Ala Val Gly His Ile Tyr  
 130 135 140

Phe Phe Leu Glu Asp Val Phe Pro Asn Gln Pro Gly Gly Ile Arg Ile  
 145 150 155 160

Leu Lys Thr Pro Ser Ile Leu Lys Ala Ile Phe Asp Thr Pro Asp Glu  
 165 170 175

Asp Pro Asn Tyr Asn Pro Leu Pro Glu Glu Arg Pro Gly Gly Phe Ala

171

180

185

190

Trp Gly Glu Gly Gln  
195

<210> 341  
<211> 108  
<212> PRT  
<213> Homo sapiens

<400> 341  
Gly Val Gly Gln Ala Thr Val Gly Lys Met Ala Tyr Gln Ser Leu Arg  
1 5 10 15  
Leu Glu Tyr Leu Gln Ile Pro Pro Val Ser Arg Ala Tyr Thr Thr Ala  
20 25 30  
Cys Val Leu Thr Thr Ala Ala Val Gln Leu Glu Leu Ile Thr Pro Phe  
35 40 45  
Gln Leu Tyr Phe Asn Pro Glu Leu Ile Phe Lys His Phe Gln Ile Trp  
50 55 60  
Arg Leu Ile Thr Asn Phe Leu Phe Phe Gly Pro Val Gly Phe Asn Phe  
65 70 75 80  
Leu Phe Asn Met Ile Phe Leu Tyr Arg Tyr Cys Arg Met Leu Glu Glu  
85 90 95  
Gly Ser Phe Arg Gly Arg Thr Ala Asp Phe Val Phe  
100 105

<210> 342  
<211> 23  
<212> PRT  
<213> Homo sapiens

<400> 342  
Leu Ile Phe Lys His Phe Gln Ile Trp Arg Leu Ile Thr Asn Phe Leu  
1 5 10 15  
Phe Phe Gly Pro Val Gly Phe  
20

<210> 343  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 343  
Phe Leu Tyr Arg Tyr Cys Arg Met Leu Glu Glu Gly Ser Phe Arg Gly  
1 5 10 15

Arg Thr Ala Asp Phe Val Phe Met Phe  
20 25

<210> 344  
<211> 23  
<212> PRT  
<213> Homo sapiens

<220>  
<221> SITE  
<222> (19)  
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 344  
Leu Val Phe Leu Gly Gln Ala Phe Thr Ile Met Leu Val Tyr Val Trp  
1 5 10 15

Ser Arg Xaa Asn Pro Tyr Val  
20

<210> 345  
<211> 21  
<212> PRT  
<213> Homo sapiens

<400> 345  
Val Leu Met Gly Phe Ser Leu Leu Leu Gly Asn Ser Ile Ile Val Asp  
1 5 10 15

Leu Leu Gly Ile Ala  
20

<210> 346  
<211> 25  
<212> PRT  
<213> Homo sapiens

<400> 346  
Asn Gln Pro Gly Gly Ile Arg Ile Leu Lys Thr Pro Ser Ile Leu Lys  
1 5 10 15

Ala Ile Phe Asp Thr Pro Asp Glu Asp  
20 25

<210> 347  
<211> 28  
<212> PRT  
<213> Homo sapiens

<400> 347

173

Arg Leu Glu Tyr Leu Gln Ile Pro Pro Val Ser Arg Ala Tyr Thr Thr  
 1 5 10 15

Ala Cys Val Leu Thr Thr Ala Ala Val Gln Leu Glu  
 20 25

&lt;210&gt; 348

&lt;211&gt; 31

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 348

Arg Leu Ile Thr Asn Phe Leu Phe Phe Gly Pro Val Gly Phe Asn Phe  
 1 5 10 15

Leu Phe Asn Met Ile Phe Leu Tyr Arg Tyr Cys Arg Met Leu Glu  
 20 25 30

&lt;210&gt; 349

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 349

His Ala Ser Ala Gly Pro Asp Gly Ser Ser Pro Ala  
 1 5 10

&lt;210&gt; 350

&lt;211&gt; 115

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 350

Glu Leu Leu Leu Glu Lys Pro Lys Pro Trp Gln Pro Pro Ala Ala Ala  
 1 5 10 15

Pro His Arg Ala Leu Leu Val Leu Cys Tyr Ser Ile Val Glu Asn Thr  
 20 25 30

Cys Ile Ile Thr Pro Thr Ala Lys Ala Trp Lys Tyr Met Glu Glu Glu  
 35 40 45

Ile Leu Gly Phe Gly Lys Ser Val Cys Asp Ser Leu Gly Arg Arg His  
 50 55 60

Met Ser Thr Cys Ala Leu Cys Asp Phe Cys Ser Leu Lys Leu Glu Gln  
 65 70 75 80

Cys His Ser Glu Ala Ser Leu Gln Arg Gln Gln Cys Asp Thr Ser His  
 85 90 95

Lys Thr Pro Phe Ala Ala Pro Cys Leu Pro Pro Arg Ala Cys Pro Ser

174

100

105

110

Ala Thr Arg  
115

<210> 351  
<211> 77  
<212> PRT  
<213> Homo sapiens

<400> 351  
Leu Pro Gly Trp Gly Phe Pro Thr Lys Ile Cys Asp Thr Asp Tyr Ile  
1 5 10 15  
Gln Tyr Pro Asn Tyr Cys Ser Phe Lys Ser Gln Gln Cys Leu Met Arg  
20 25 30  
Asn Arg Asn Arg Lys Val Ser Arg Met Arg Cys Leu Gln Asn Glu Thr  
35 40 45  
Tyr Ser Ala Leu Ser Pro Gly Lys Ser Glu Asp Val Val Leu Arg Trp  
50 55 60  
Ser Gln Glu Phe Ser Thr Leu Thr Leu Gly Gln Phe Gly  
65 70 75

<210> 352  
<211> 65  
<212> PRT  
<213> Homo sapiens

<400> 352  
Ser Pro Val Leu Leu Pro Ala Phe Pro Pro Leu Pro Val Pro Leu Leu  
1 5 10 15  
Ala Leu Pro Val Ser Ala Pro Leu Pro Ala Cys Val Leu Val Ser Ala  
20 25 30  
Pro Ala Cys Ala Pro Leu Leu Ala Pro Ala Cys Ala Leu Ala Leu Ala  
35 40 45  
Pro Gly Phe Pro Gly Thr Arg Arg Ile Val Gly Ala Leu Pro Arg Cys  
50 55 60  
Cys  
65

<210> 353  
<211> 35  
<212> PRT  
<213> Homo sapiens



175

&lt;400&gt; 353

Leu Leu Val Leu Cys Tyr Ser Ile Val Glu Asn Thr Cys Ile Ile Thr  
1 5 10 15

Pro Thr Ala Lys Ala Trp Lys Tyr Met Glu Glu Glu Ile Leu Gly Phe  
20 25 30

Gly Lys Ser  
35

&lt;210&gt; 354

&lt;211&gt; 26

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 354

Leu Lys Leu Glu Gln Cys His Ser Glu Ala Ser Leu Gln Arg Gln Gln  
1 5 10 15

Cys Asp Thr Ser His Lys Thr Pro Phe Ala  
20 25

&lt;210&gt; 355

&lt;211&gt; 40

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 355

Gln Val Ser Gly Leu Ile Leu Ser Leu Ser Cys Gly Met Asp Gly Leu  
1 5 10 15

Ala Leu Asp Gly Ser Pro Ser Pro Ser Pro Xaa Thr Glu Lys Ala Gly  
20 25 30

Arg Cys Ile Ser Gln Thr Ser Leu  
35 40

&lt;210&gt; 356

&lt;211&gt; 46

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (27)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

176

&lt;400&gt; 356

Gln Val Ser Gly Leu Ile Leu Ser Leu Ser Cys Gly Met Asp Gly Leu  
 1 5 10 15

Ala Leu Asp Gly Ser Pro Ser Pro Ser Pro Xaa Thr Glu Lys Ala Gly  
 20 25 30

Arg Cys Ile Ser Gln Thr Ser Leu Pro Gly Lys Trp Glu Val  
 35 40 45

&lt;210&gt; 357

&lt;211&gt; 173

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (118)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 357

Arg Ala Ser Lys Thr Val Pro Arg Met Pro Pro Asn Trp Pro Ala Lys  
 1 5 10 15

Met Pro Cys Leu Cys His Ile Arg Thr Val Glu His Leu Gly Thr Ile  
 20 25 30

Ser Ser Gly Ala Pro Gly Arg Pro Thr Gly Gln Gln Ala Ala Arg Thr  
 35 40 45

Tyr His Ile Cys Trp Ile His Pro Gly Gln Lys Ile Asp Ser Leu Pro  
 50 55 60

Pro Ser Ser Gln His Pro Arg Ser Gln Gln Leu Ala Pro Gly Thr Trp  
 65 70 75 80

Pro Ser Thr Ser Thr Thr Lys Pro Ala Glu Glu Thr Leu Gly Ser Ser  
 85 90 95

Ala Ser Leu Pro Ile Ser Gln Ala Arg Lys Ser Glu Lys Cys Thr Phe  
 100 105 110

Gln Pro Ser Pro Trp Xaa Val Arg Gly Lys Glu Ser His Gln Val Pro  
 115 120 125

Ala His Pro Ser His Arg Thr Glu Thr Glu Ser Asp His Ser Pro Val  
 130 135 140

Arg Lys Pro Pro Ser Arg Gly Thr Arg Thr Gly Asp Phe Thr Val Gly  
 145 150 155 160

Asp Trp Ser Glu Ala Trp Leu Leu Glu Leu Ala Leu Leu  
 165 170

177

&lt;210&gt; 358

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 358

Arg Met Pro Pro Asn Trp Pro Ala Lys Met Pro Cys Leu Cys His Ile  
1 5 10 15

Arg Thr Val Glu His Leu Gly  
20

&lt;210&gt; 359

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 359

Gly Arg Pro Thr Gly Gln Gln Ala Ala Arg Thr Tyr His Ile Cys Trp  
1 5 10 15

Ile His Pro Gly Gln Lys Ile Asp Ser  
20 25

&lt;210&gt; 360

&lt;211&gt; 25

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 360

Trp Pro Ser Thr Ser Thr Thr Lys Pro Ala Glu Glu Thr Leu Gly Ser  
1 5 10 15

Ser Ala Ser Leu Pro Ile Ser Gln Ala  
20 25

&lt;210&gt; 361

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (13)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 361

Lys Ser Glu Lys Cys Thr Phe Gln Pro Ser Pro Trp Xaa Val Arg Gly  
1 5 10 15

Lys Glu Ser His Gln Val Pro

20

<210> 362  
<211> 24  
<212> PRT  
<213> Homo sapiens

<400> 362  
Lys Pro Pro Ser Arg Gly Thr Arg Thr Gly Asp Phe Thr Val Gly Asp  
1 5 10 15

Trp Ser Glu Ala Trp Leu Leu Glu  
20

<210> 363  
<211> 10  
<212> PRT  
<213> Homo sapiens

<400> 363  
Pro Cys Ala Asp Cys Leu Ser Ala Trp Ala  
1 5 10

<210> 364  
<211> 11  
<212> PRT  
<213> Homo sapiens

<400> 364  
His Ala Ser Gly Tyr Leu Cys Ile Val Leu Leu  
1 5 10

<210> 365  
<211> 34  
<212> PRT  
<213> Homo sapiens

<400> 365  
Asn Ser Ala Arg Ala Ala Arg Ala Glu Ile Val Leu Gly Leu Leu Val  
1 5 10 15

Trp Thr Leu Ile Ala Gly Thr Glu Tyr Phe Arg Val Pro Ala Phe Gly  
20 25 30

Trp Val

<210> 366  
<211> 22  
<212> PRT

<213> Homo sapiens

<400> 366

Pro Cys Ser Pro Pro Asp Ser Pro Pro Leu Pro Gly Ala Phe Val Trp  
1 5 10 15

Arg Val Leu Trp Val Cys  
20

<210> 367

<211> 25

<212> PRT

<213> Homo sapiens

<400> 367

Ala Arg Ala Cys Phe Ala Tyr Asn Gly Val Cys Ser Glu Gly Arg Cys  
1 5 10 15

Trp Asp Ser His Phe His Gly Ser Val  
20 25

<210> 368

<211> 100

<212> PRT

<213> Homo sapiens

<400> 368

Met Ser Asn Met Gly Lys Ile Pro Ser Leu Ser Leu His Ile Pro Ile  
1 5 10 15

Asn Lys Tyr Ile Cys Ser Arg Ile Pro Lys Phe Ile Gln Lys Val Asn  
20 25 30

Lys Ser Thr Val Leu Gln Ile Cys Leu Lys Arg Gln Ile Ile Leu Asn  
35 40 45

Lys Asn Lys Met Ser Asp His Ser Lys Ile Gly Lys Ala Asn Leu Val  
50 55 60

Gln Ile Asp Ile His Ser Leu Gly Ile Val Glu Thr Gly Cys Val Pro  
65 70 75 80

Ser Lys Arg Tyr Cys Thr Leu Leu Thr Glu Gln Ser Gly Phe Pro Phe  
85 90 95

Leu Ser His Pro  
100

<210> 369

<211> 84

<212> PRT

<213> Homo sapiens

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (54)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (58)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;220&gt;

&lt;221&gt; SITE

&lt;222&gt; (82)

&lt;223&gt; Xaa equals any of the naturally occurring L-amino acids

&lt;400&gt; 369

Met	Ala	Gly	Cys	Cys	Leu	Lys	Leu	Phe	Gly	Val	Leu	Ser	Leu	Cys	Phe
1				5					10					15	

Leu	Cys	Gly	Leu	Ile	Ser	Ile	Glu	Arg	Val	Ile	Cys	Asn	Pro	Val	Ser
			20					25					30		

Ala	Asp	Phe	Gln	Val	Ser	Thr	Phe	Cys	Gln	Arg	His	Cys	Leu	Leu	Arg
		35					40					45			

Ser	Lys	Val	Met	Phe	Xaa	Ile	Lys	Gly	Xaa	Thr	Ala	Thr	Ile	Glu	Val
	50					55					60				

Ile	Asn	Glu	Asn	Cys	Thr	Leu	Val	Ala	Ala	Pro	Pro	Ile	Gly	Phe	Pro
65					70					75					80

Ile Xaa Phe Leu

&lt;210&gt; 370

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 370

Met	Ser	Asp	His	Ser	Lys	Ile	Gly	Lys	Ala	Asn	Leu	Val	Gln	Ile	Asp
1				5				10					15		

Ile	His	Ser	Leu	Gly	Ile	Val	Glu	Thr	Gly	Cys	Val	Pro	Ser	Lys	Arg
			20					25				30			

Tyr	Cys	Thr	Leu	Leu	Thr	Glu	Gln	Ser	Gly	Phe	Pro	Phe	Leu	Ser	His
		35					40					45			

Pro

181

<210> 371  
 <211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 371  
 Met Ala Gly Cys Cys Leu Lys Leu Phe Gly Val Leu Ser Leu Cys Phe  
           1                  5                  10                  15  
 Leu Cys Gly Leu Ile Ser Ile Glu Arg Val Ile Cys Asn Pro Val Ser  
                   20                  25                  30  
 Ala Asp Phe Gln Val Ser Thr Phe Cys Gln Arg His Cys Leu Leu Arg  
           35                  40                  45  
 Ser Lys  
       50

<210> 372  
 <211> 34  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (4)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (8)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>  
 <221> SITE  
 <222> (32)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 372  
 Val Met Phe Xaa Ile Lys Gly Xaa Thr Ala Thr Ile Glu Val Ile Asn  
           1                  5                  10                  15  
 Glu Asn Cys Thr Leu Val Ala Ala Pro Pro Ile Gly Phe Pro Ile Xaa  
           20                  25                  30

Phe Leu

<210> 373  
 <211> 65  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 373

Pro Thr Glu Gly Arg Gln Lys Val Leu Lys Thr Phe Thr Val Pro Arg  
 1 5 10 15

Ser Ala Leu Ala Met Thr Lys Thr Ser Thr Cys Ile Tyr His Phe Leu  
 20 25 30

Val Leu Ser Trp Tyr Thr Phe Leu Asn Tyr Tyr Ile Ser Gln Glu Gly  
 35 40 45

Lys Asp Glu Val Lys Pro Lys Ile Leu Ala Asn Gly Ala Arg Trp Lys  
 50 55 60

Tyr  
 65

&lt;210&gt; 374

&lt;211&gt; 35

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 374

Pro Arg Ser Ala Leu Ala Met Thr Lys Thr Ser Thr Cys Ile Tyr His  
 1 5 10 15

Phe Leu Val Leu Ser Trp Tyr Thr Phe Leu Asn Tyr Tyr Ile Ser Gln  
 20 25 30

Glu Gly Lys  
 35

&lt;210&gt; 375

&lt;211&gt; 24

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 375

Pro Thr Glu Gly Arg Gln Lys Val Leu Lys Thr Phe Thr Val Pro Arg  
 1 5 10 15

Ser Ala Leu Ala Met Thr Lys Thr  
 20

&lt;210&gt; 376

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 376

Phe Leu Asn Tyr Tyr Ile Ser Gln Glu Gly Lys Asp Glu Val Lys Pro  
 1 5 10 15



183

Lys Ile Leu Ala Asn Gly Ala Arg Trp Lys Tyr  
                   20                  25

<210> 377  
 <211> 13  
 <212> PRT  
 <213> Homo sapiens

<400> 377  
 Phe Lys Asp Gln Leu Val Tyr Pro Leu Leu Ala Phe Thr  
      1                  5                  10

<210> 378  
 <211> 13  
 <212> PRT  
 <213> Homo sapiens

<400> 378  
 Arg Gln Ala Leu Asn Leu Pro Asp Val Phe Gly Leu Val  
      1                  5                  10

<210> 379  
 <211> 10  
 <212> PRT  
 <213> Homo sapiens

<400> 379  
 Ala Thr Ala Ser His Asp Leu Leu Leu Phe  
      1                  5                  10

<210> 380  
 <211> 97  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (72)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 380  
 Met Ser Ile Asn Ile Cys Leu Met Gln Ser Lys Thr Gln Gly Ser Cys  
      1                  5                  10                  15

Gln Tyr Leu Leu Leu Pro His Pro Val Pro Ile Ile Leu Lys Val Ser  
           20                  25                  30

Thr Val Phe Ser Leu Leu Ser Leu Phe Arg Leu Leu Phe Leu Ser Phe  
           35                  40                  45

Cys Pro His Pro Lys Lys Cys Ser Tyr Leu Leu Lys Tyr Tyr Gly Pro

184

50                      55                      60  
 Leu Glu Gly His Lys Thr Leu Xaa Tyr Leu Arg Thr Asn Leu Gly Val  
 65                      70                      75                      80  
 Ile Gln Pro Pro Leu Arg Met Tyr Ala Ala Glu Asp Cys Asn Gly Ile  
                     85                      90                      95

Gly

<210> 381  
 <211> 46  
 <212> PRT  
 <213> Homo sapiens

<400> 381  
 Met Ser Ile Asn Ile Cys Leu Met Gln Ser Lys Thr Gln Gly Ser Cys  
 1                      5                      10                      15  
 Gln Tyr Leu Leu Leu Pro His Pro Val Pro Ile Ile Leu Lys Val Ser  
                     20                      25                      30  
 Thr Val Phe Ser Leu Leu Ser Leu Phe Arg Leu Leu Phe Leu  
                     35                      40                      45

<210> 382  
 <211> 51  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> SITE  
 <222> (26)  
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 382  
 Ser Phe Cys Pro His Pro Lys Lys Cys Ser Tyr Leu Leu Lys Tyr Tyr  
 1                      5                      10                      15  
 Gly Pro Leu Glu Gly His Lys Thr Leu Xaa Tyr Leu Arg Thr Asn Leu  
                     20                      25                      30  
 Gly Val Ile Gln Pro Pro Leu Arg Met Tyr Ala Ala Glu Asp Cys Asn  
                     35                      40                      45

Gly Ile Gly  
 50

<210> 383  
 <211> 23  
 <212> PRT

185

&lt;213&gt; Homo sapiens

&lt;400&gt; 383

Lys Glu Glu Asp Asp Asp Thr Glu Arg Leu Pro Ser Lys Cys Glu Val  
1 5 10 15

Cys Lys Leu Leu Ser Thr Glu  
20

&lt;210&gt; 384

&lt;211&gt; 23

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 384

Lys Glu Glu Asp Asp Asp Thr Glu Arg Leu Pro Ser Lys Cys Glu Val  
1 5 10 15

Cys Lys Leu Leu Ser Thr Glu  
20

&lt;210&gt; 385

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 385

Leu Gln Ala Glu Leu Ser Arg Thr Gly Arg Ser Arg Glu Val Leu Glu  
1 5 10 15

Leu Gly Gln

&lt;210&gt; 386

&lt;211&gt; 19

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 386

Leu Gln Ala Glu Leu Ser Arg Thr Gly Arg Ser Arg Glu Val Leu Glu  
1 5 10 15

Leu Gly Gln

&lt;210&gt; 387

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 387

186

Arg Gln Ala Val Ile Val Cys Arg Arg Arg Phe Val  
 1 5 10

&lt;210&gt; 388

&lt;211&gt; 148

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 388

Pro Pro Arg Trp Ala His Pro Lys Ala Pro Glu Gly Ser Pro Asp Pro  
 1 5 10 15

Pro Ser Pro Pro Ser Ala Leu Gly Leu Ser Val Leu Pro Trp Ser Asp  
 20 25 30

Ser Asp Pro Trp His Ile Ser Val Ser Pro Cys Ala Gln Arg Glu His  
 35 40 45

Tyr Ser Pro Gly Ser Ala His Ile Asn Ser Leu Arg Pro Leu Pro Ala  
 50 55 60

Leu Ser Leu Lys Arg Cys Lys Ala Arg Val Ser Ser Ser Cys Leu Tyr  
 65 70 75 80

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Glu Ile Asp Arg Cys Asp  
 85 90 95

Ser Val Pro Pro Val Ala Leu Cys Ser Ala Ala Tyr Thr Leu Arg Ile  
 100 105 110

Cys Trp Ala Ser Val Leu Cys His Arg Pro Pro Pro Ser Thr Ser Gln  
 115 120 125

Pro Lys Pro Arg Ala Arg Pro Lys Lys Gly Lys Ala Ile Phe Pro Thr  
 130 135 140

Ala Gln Val Pro  
 145

&lt;210&gt; 389

&lt;211&gt; 71

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 389

Pro Pro Arg Trp Ala His Pro Lys Ala Pro Glu Gly Ser Pro Asp Pro  
 1 5 10 15

Pro Ser Pro Pro Ser Ala Leu Gly Leu Ser Val Leu Pro Trp Ser Asp  
 20 25 30

Ser Asp Pro Trp His Ile Ser Val Ser Pro Cys Ala Gln Arg Glu His  
 35 40 45

Tyr Ser Pro Gly Ser Ala His Ile Asn Ser Leu Arg Pro Leu Pro Ala  
 50 55 60

Leu Ser Leu Lys Arg Cys Lys  
 65 70

<210> 390  
 <211> 77  
 <212> PRT  
 <213> Homo sapiens

<400> 390  
 Ala Arg Val Ser Ser Ser Cys Leu Tyr Pro Ala Pro Ala Pro Ala Pro  
 1 5 10 15

Ala Pro Leu Glu Ile Asp Arg Cys Asp Ser Val Pro Pro Val Ala Leu  
 20 25 30

Cys Ser Ala Ala Tyr Thr Leu Arg Ile Cys Trp Ala Ser Val Leu Cys  
 35 40 45

His Arg Pro Pro Pro Ser Thr Ser Gln Pro Lys Pro Arg Ala Arg Pro  
 50 55 60

Lys Lys Gly Lys Ala Ile Phe Pro Thr Ala Gln Val Pro  
 65 70 75

<210> 391  
 <211> 26  
 <212> PRT  
 <213> Homo sapiens

<400> 391  
 Glu Glu Lys Leu Phe Thr Ser Ala Pro Gly Arg Asp Phe Trp Val Met  
 1 5 10 15

Gly Glu Thr Arg Asp Gly Asn Glu Glu Asn  
 20 25

<210> 392  
 <211> 42  
 <212> PRT  
 <213> Homo sapiens

<400> 392  
 Gln Lys Pro Thr Phe Ala Leu Gly Glu Leu Tyr Pro Pro Leu Ile Asn  
 1 5 10 15

Leu Trp Glu Ala Gly Lys Glu Lys Ser Thr Ser Leu Lys Val Lys Ala  
 20 25 30

Thr Val Ile Gly Leu Pro Thr Asn Met Ser  
35 40

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/05804**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.5; 435/320.1, 252.3, 69.1, 6, 7.1; 530/300, 388.22; 514/2; 436/501

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Database EST: Accession No.:AA331279. ADAMS et al. Initial assessment of human gene diversity and expression patterns based upon 83 million nucleotides of cDNA sequence. Nature 377 (6547 Suppl), 3-174 (1995). Nucleotides 1-314.	1-12, 14-21
A	SCHWARTING, R. et al. Biochemical characterization and purification of human B Cell Stimulatory Factor (BSF). Eur. J. Immunol. 1985, Vol. 15, pages 632-637, see entire document.	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 JUNE 1999

Date of mailing of the international search report

07 JUL 1999

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

EILEEN O'HARA

Telephone No. (703) 308-0196

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/05804

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/05804

## A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C07H 21/04; C07K 1/00, 16/00; C12N 15/00, 1/20; C12P 21/06; A61K 38/00; C12Q 1/68; G01N 33/53, 33/566

## A. CLASSIFICATION OF SUBJECT MATTER: US CL :

536/23.5; 435/320.1, 252.3, 69.1, 6, 7.1; 530/300, 388.22; 514/2; 436/501

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

SEQUENCE DATA BASE MPSRCH: EST, GenEmbl, N\_Geneseq\_34, Issued Patents\_NA, SPTREMBL\_8, SwissProt\_36, PIR\_58, Issued Patents\_AA, (SEQ ID NOS: 11 and 108 only). One nucleotide sequence and one amino acid sequence have been searched. It is not clear which sequences are embraced by the claims because the claims refer to sequences X and Y. The table at pages 180-188 contains many sequences X and Y, yet the claims refer to X and Y in the singular only. Accordingly, the first X nucleotide sequence disclosed and the first Y amino acid sequence disclosed were searched.

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-21, drawn to nucleic acid molecules, vectors, host cells containing recombinant nucleic acid molecules, polypeptides, antibodies, a method of producing a polypeptide, a method for treating a medical condition comprising administering a polypeptide, a method of diagnosing a pathological condition by genetic analysis or protein assay, and a method for identifying a binding partner to a polypeptide, for gene 1, the nucleic acid molecule identified by SEQ ID NO:11, and the polypeptide identified by SEQ ID NO: 108, as listed in the table on pages 180-188 of the description. Groups II through XCV, claims 1-21 for each group, drawn to nucleic acid molecules, vectors, host cells containing recombinant nucleic acid molecules, polypeptides, antibodies, a method of producing a polypeptide, a method for treating a medical condition comprising administering a polypeptide, a method of diagnosing a pathological condition by genetic analysis or protein assay, and a method for identifying a binding partner to a polypeptide for, genes 2 through 95, the nucleic acid molecules identified by SEQ ID NOS:12 through 105, and the polypeptides identified by SEQ ID NOS:109 through 202 respectively, as listed in the table on pages 180-188 of the description.

The inventions listed as Groups I through XCV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Pursuant to 37 C.F.R. § 1.475(b-d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto.

Pursuant to 37 C.F.R. § 1.475(b-d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first recited product, a polynucleotide comprising gene No. 1, identified by SEQ ID NO:11, the polypeptide it encodes, identified by SEQ ID NO:108, methods of producing the polypeptide, and methods of using the polynucleotide and polypeptide. Further pursuant to 37 C.F.R. § 1.475(b-d), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

**THIS PAGE BLANK (USPTO)**